09/980,593

PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 207/27, A61K 31/40, C07D 401/12, 417/12

A1

(11) International Publication Number: WO 99/18074

(43) International Publication Date: 15 April 1999 (15.04.99)

(21) International Application Number: PCT/US98/21037

(22) International Filing Date: 2 October 1998 (02.10.98)

(30) Priority Data:
60/062,418 3 October 1997 (03.10.97) US

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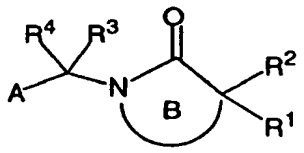
(81) Designated States: AU, BR, CA, CN, CZ, EE, HU, IL, JP, KR, LT, LV, MX, NO, NZ, PL, RO, SG, SI, SK, UA, VN, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: NOVEL LACTAM METALLOPROTEASE INHIBITORS



(I)

(57) Abstract

The present application describes novel lactams and derivatives thereof of formula (I), or pharmaceutically acceptable salt forms thereof, wherein ring B is a 4–8 membered cyclic amide containing from 0–3 additional heteroatoms selected from N, O, and S, which are useful as metalloprotease inhibitors.

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TITLE

Novel Lactam Metalloprotease Inhibitors

FIELD OF THE INVENTION

This invention relates generally to novel lactam metalloprotease inhibitors, pharmaceutical compositions containing the same, and methods of using the same.

BACKGROUND OF THE INVENTION

There is now a body of evidence that metalloproteinases (MP) are important in the uncontrolled breakdown of connective tissue, including proteoglycan and collagen, leading to resorption of the extracellular matrix. This is a feature of many pathological conditions, such as rheumatoid and osteoarthritis, corneal, epidermal or gastric ulceration; tumor metastasis or invasion; periodontal disease and bone disease. Normally these catabolic enzymes are tightly regulated at the level of their synthesis as well as at their level of extracellular activity through the action of specific inhibitors, such as alpha-2-macroglobulins and TIMP (tissue inhibitor of metalloproteinase), which form inactive complexes with the MP's.

Osteo- and Rheumatoid Arthritis (OA and RA respectively) are destructive diseases of articular cartilage characterized by localized erosion of the cartilage surface. Findings have shown that articular cartilage from the femoral heads of patients with OA, for example, had a reduced incorporation of radiolabeled sulfate over controls, suggesting that there must be an enhanced rate of cartilage degradation in OA (Mankin et al. J. Bone Joint Surg. 52A, 1970, 424-434). There are four classes of protein degradative enzymes in mammalian cells: serine, cysteine, aspartic and metalloproteinases. The available evidence supports that it is the metalloproteinases which are responsible for the degradation of the extracellular matrix of articullar cartillage in OA and RA. Increased activities of collagenases and stromelysin have been found in OA cartilage and the activity correlates with severity of the

lesion (Mankin et al. Arthritis Rheum. 21, 1978, 761-766, Woessner et al. Arthritis Rheum. 26, 1983, 63-68 and Ibid. 27, 1984, 305-312). In addition, aggrecanase (a newly identified metalloproteinase enzymatic activity) has been identified that provides the specific cleavage product of proteoglycan, found in RA and OA patients (Lohmander L.S. et al. Arthritis Rheum. 36, 1993, 1214-22).

Therefore metalloproteinases (MP) have been implicated as the key enzymes in the destruction of mammalian cartilage and bone. It can be expected that the pathogenesis of such diseases can be modified in a beneficial manner by the administration of MP inhibitors, and many compounds have been suggested for this purpose (see Wahl et al. Ann. Rep. Med. Chem. 25, 175-184, AP, San Diego, 1990).

Tumor necrosis factor (TNF) is a cell associated cytokine that is processed from a 26kd precursor form to a 17kd active form. TNF has been shown to be a primary mediator in humans and in animals, of inflammation, fever, and acute phase responses, similar to those observed during acute infection and shock. Excess TNF has been shown to be lethal. There is now considerable evidence that blocking the effects of TNF with specific antibodies can be beneficial in a variety of circumstances including autoimmune diseases such as rheumatoid arthritis (Feldman et al, Lancet, 1994, 344, 1105) and non-insulin dependent diabetes melitus. (Lohmander L.S. et al. Arthritis Rheum. 36, 1993, 1214-22) and Crohn's disease (Macdonald T. et al. Clin. Exp. Immunol. 81, 1990, 301) .

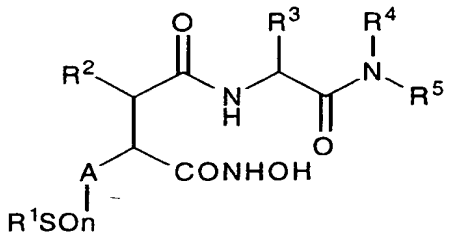
Compounds which inhibit the production of TNF are therefore of therapeutic importance for the treatment of inflammatory disorders. Recently it has been shown that a matrix metalloproteinase or family of metalloproteinases, hereafter known as TNF-convertases (TNF-C), as well as other MP's are capable of cleaving TNF from its inactive to active form (Gearing et al Nature, 1994, 370, 555). This invention describes molecules that inhibit this conversion and hence the secretion of active TNF-a from cells. These novel molecules provide a means of mechanism based therapeutic intervention for diseases including but not restricted to septic shock,

haemodynamic shock, sepsis syndrom, post ischaemic reperfusion injury, malaria, Crohn's disease, inflammatory bowel diseases, mycobacterial infection, meningitis, psoriasis, congestive heart failure, fibrotic diseases, cachexia, graft rejection, cancer, diseases involving angiogenesis, autoimmune diseases, skin inflammatory diseases, osteo and rheumatoid arthritis, multiple sclerosis, radiation damage, hyperoxic alveolar injury, periodontal disease, HIV and non-insulin dependent diabetes melitus.

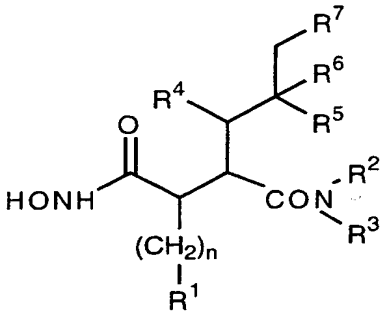
Since excessive TNF production has been noted in several disease conditions also charactarized by MMP-mediated tissue degradation, compounds which inhibit both MMPs and TNF production may also have a particular advantage in diseases where both mechansisms are involved.

There are several patents which disclose hydroxamate and carboxylate based MMP inhibitors.

WO95/09841 describes compounds that are hydroxamic acid derivatives and are inhibitors of cytokine production.



European Patent Application Publication No. 574,758 A1, discloses hydroxamic acid derivatives as collagenase inhibitors having the general formula:



GB 2 268 934 A and WO 94/24140 claim hydroxamate inhibitors of MMPs as inhibitors of TNF production.

The compounds of the current invention act as inhibitors of MMPs, in particular aggrecanase and TNF. These novel molecules are provided as anti-inflammatory compounds and cartilage protecting therapeutics. The inhibiton of aggrecanase, TNF-C, and other metalloproteinases by molecules of the present invention indicates they are anti-inflammatory and should prevent the degradation of cartilage by these enzymes, thereby alleviating the pathological conditions of osteo- and rheumatoid arthritis.

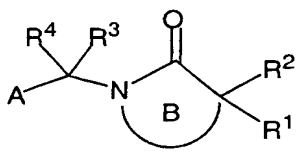
SUMMARY OF THE INVENTION

Accordingly, one object of the present invention is to provide novel lactams which are useful as metalloprotease inhibitors or pharmaceutically acceptable salts or prodrugs thereof.

It is another object of the present invention to provide pharmaceutical compositions comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

It is another object of the present invention to provide a method for treating inflammatory disorders comprising administering to a host in need of such treatment a therapeutically effective amount of at least one of the compounds of the present invention or a pharmaceutically acceptable salt or prodrug form thereof.

These and other objects, which will become apparent during the following detailed description, have been achieved by the inventors' discovery that compounds of formula (I):

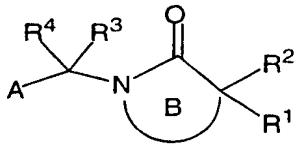


I

or pharmaceutically acceptable salt or prodrug forms thereof, wherein A, B, R^1, R^2, R^3, and R^4 are defined below, are effective metalloprotease inhibitors.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

[1] Thus, in a first embodiment, the present invention provides a novel compound of formula I:



I

or a stereoisomer or pharmaceutically acceptable salt form thereof, wherein;

A is selected from COR^5, $-CO_2H$, CH_2CO_2H, $-CO_2R^6$, $-CONHOH$, $-CONHOR^5$, $-CONHOR^6$, $-NHR^a$, $-N(OH)COR^5$, $-SH$, $-CH_2SH$, $-SO_2NHR^a$, $SN_2H_2R^a$, $PO(OH)_2$, and $PO(OH)NHR^a$;

ring B is a 4-8 membered cyclic amide containing from 0-3 additional heteroatoms selected from O, NR^a, and $S(O)_p$, 0-1 additional carbonyl groups and 0-1 double bonds;

R^1 is $U-X-Y-Z-U^a-X^a-Y^a-Z^a$;

U is absent or is selected from: O, NR^a, C(O), C(O)O, OC(O), $C(O)NR^a$, $NR^aC(O)$, OC(O)O, $OC(O)NR^a$, $NR^aC(O)O$, $NR^aC(O)NR^a$, $S(O)_p$, $S(O)_pNR^a$, $NR^aS(O)_p$, and $NR^aSO_2NR^a$;

X is absent or selected from C_{1-10} alkylene, C_{2-10} alkenylene, and C_{2-10} alkynylene;

Y is absent or selected from O, NR^a, $S(O)_p$, and C(O);

Z is absent or selected from a C_{3-13} carbocyclic residue substituted with 0-5 R^b and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the

group consisting of N, O, and S and substituted with 0-5 R^b;

U^a is absent or is selected from: O, NR^a, C(O), C(O)O, OC(O), $C(O)NR^a$, $NR^aC(O)$, OC(O)O, $OC(O)NR^a$, $NR^aC(O)O$, $NR^aC(O)NR^a$, $S(O)_p$, $S(O)_pNR^a$, $NR^aS(O)_p$, and $NR^aSO_2NR^a$;

X^a is absent or selected from C_{1-10} alkylene, C_{2-10} alkenylene, C_{2-10} alkynylene;

Y^a is absent or selected from O, NR^a, $S(O)_p$, and C(O);

Z^a is selected from H, a C_{3-13} carbocyclic residue substituted with 0-5 R^c and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c;

R^2 is selected from H, Q', C_{1-10} alkylene-Q', C_{2-10} alkenylene-Q', C_{2-10} alkynylene-Q', $(CRR')_r$,$O(CRR')_r$-Q', $(CRR')_r$,$NR^a(CRR')_r$-Q', $(CRR')_r$,$NR^aC(O)(CRR')_r$-Q', $(CRR')_r$,$C(O)NR^a(CRR')_r$-Q', $(CRR')_r$,$C(O)(CRR')_r$-Q', $(CRR')_r$,$C(O)O(CRR')_r$-Q', $(CRR')_r$,$S(O)_p(CRR')_r$-Q', $(CRR')_r$,$SO_2NR^a(CRR')_r$-Q', $(CRR')_r$,$NR^aC(O)NR^a(CRR')_r$-Q', $(CRR')_r$,$OC(O)NR^a(CRR')_r$-Q', and $(CRR')_r$,$NR^aC(O)O(CRR')_r$-Q';

R, at each occurrence, is independently selected from H, CH_3, CH_2CH_3, $CH=CH_2$, $CH=CHCH_3$, and $CH_2CH=CH_2$;

R', at each occurrence, is independently selected from H, CH_3, CH_2CH_3, and $CH(CH_3)_2$;

alternatively, R^1 and R^2 combine to form a C_{3-13} carbocyclic residue substituted with $R^{1'}$ and 0-3 R^b or a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with $R^{1'}$ and 0-3 R^b;

Q' is selected from H, a C_{3-13} carbocyclic residue substituted with 0-5 R^b and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^b;

$R^{1'}$ is U^a-X^a-Y^a-Z^a;

R^3 is selected from H, Q, C_{1-10} alkylene-Q, C_{2-10} alkenylene-Q, C_{2-10} alkynylene-Q, $(CRR')_r O(CRR')_r$-Q, $(CRR')_r NR^a(CRR')_r$-Q, $(CRR')_r C(O)(CRR')_r$-Q, $(CRR')_r C(O)O(CRR')_r$-Q, $(CRR')_r OC(O)(CRR')_r$-Q, $(CRR')_r C(O)NR^a(CRR')_r$-Q, $(CRR')_r NR^a C(O)(CRR')_r$-Q, $(CRR')_r OC(O)O(CRR')_r$-Q, $(CRR')_r OC(O)NR^a(CRR')_r$-Q, $(CRR')_r NR^a C(O)O(CRR')_r$-Q, $(CRR')_r NR^a C(O)NR^a(CRR')_r$-Q, $(CRR')_r S(O)_p(CRR')_r$-Q, $(CRR')_r SO_2NR^a(CRR')_r$-Q, $(CRR')_r NR^a SO_2(CRR')_r$-Q, $(CRR')_r NR^a SO_2NR^a(CRR')_r$-Q, $(CRR')_r NR^a C(O)(CRR')_r$"NHQ, $(CRR')_r NR^a C(O)(CRR')_r NHC(O)OR^a$, and $(CRR')_r NR^a C(O)(CRR')_r NHC(O)(CRR')_r NHC(O)OR^a$,

Q is selected from H, a C_{3-13} carbocyclic residue substituted with 0-5 R^b and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^b;

R^4 is selected from H, C_{1-10} alkylene-H, C_{2-10} alkenylene-H, C_{2-10} alkynylene-H, $(CRR')_r O(CRR')_r$-H, $(CRR')_r NR^a(CRR')_r$-H, $(CRR')_r C(O)(CRR')_r$-H, $(CRR')_r C(O)O(CRR')_r$-H, $(CRR')_r OC(O)(CRR')_r$-H, $(CRR')_r C(O)NR^a(CRR')_r$-H, $(CRR')_r NR^a C(O)(CRR')_r$-H, $(CRR')_r OC(O)O(CRR')_r$-H, $(CRR')_r OC(O)NR^a(CRR')_r$-H, $(CRR')_r NR^a C(O)O(CRR')_r$-H, $(CRR')_r NR^a C(O)NR^a(CRR')_r$-H, $(CRR')_r S(O)_p(CRR')_r$-H, $(CRR')_r SO_2NR^a(CRR')_r$-H, $(CRR')_r NR^a SO_2(CRR')_r$-H, and $(CRR')_r NR^a SO_2NR^a(CRR')_r$-H;

alternatively, R^3 and R^4 combine to form a C_{3-13} carbocyclic residue substituted with $R^{1'}$ and 0-3 R^b or a 5-14 membered heterocyclic system containing from 1-4

heteroatoms selected from the group consisting of N, O, and S and substituted with $R^{1'}$ and 0-3 R^b;

R^a, at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl and benzyl;

$R^{a'}$, at each occurrence, is independently selected from H, C_{1-4} alkyl, phenyl and benzyl;

$R^{a''}$, at each occurrence, is independently selected from H, C_{1-4} alkyl, benzyl, C_{3-7} carbocyclic residue, or a 5 to 6 membered heteroaromatic ring containing 1-4 heteroatoms selected from the group consisting of N, O, and S;

alternatively, R^a and $R^{a'}$ taken together with the nitrogen to which they are attached form a 5 or 6 membered ring containing from 0-1 additional heteroatoms selected from the group consisting of N, O, and S;

R^b, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^{a''}$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $S(O)_pR^a$, CF_3, and CF_2CF_3;

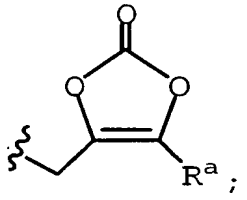
R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $NR^aC(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $S(O)_pR^a$, CF_3, CF_2CF_3, -CH(=NOH), $-C(=NOH)CH_3$, $(CRR')_sO(CRR')_{s'}R^d$, $(CRR')_sS(O)_p(CRR')_{s'}R^d$, $(CRR')_sNR^a(CRR')_{s'}R^d$, phenyl, and a 5-14 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S;

R^5, at each occurrence, is selected from C_{1-10} alkyl substituted with 0-2 R^b, and C_{1-8} alkyl substituted with 0-2 R^d;

R^d, at each occurrence, is independently selected from phenyl substituted with 0-3 R^b, biphenyl substituted with 0-2

R^b, naphthyl substituted with 0-3 R^b and a 5-10 membered heteroaryl system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R^b;

R^6, at each occurrence, is selected from phenyl, naphthyl, C_{1-10} alkyl-phenyl-C_{1-6} alkyl-, C_{3-11} cycloalkyl, C_{1-6} alkylcarbonyloxy-C_{1-3} alkyl-, C_{1-6} alkoxycarbonyloxy-C_{1-3} alkyl-, C_{2-10} alkoxycarbonyl, C_{3-6} cycloalkylcarbonyloxy-C_{1-3} alkyl-, C_{3-6} cycloalkoxycarbonyloxy-C_{1-3} alkyl-, C_{3-6} cycloalkoxycarbonyl, phenoxycarbonyl, phenyloxycarbonyloxy-C_{1-3} alkyl-, phenylcarbonyloxy-C_{1-3} alkyl-, C_{1-6} alkoxy-C_{1-6} alkylcarbonyloxy-C_{1-3} alkyl-, [5-(C_{1-5} alkyl)-1,3-dioxa-cyclopenten-2-one-yl]methyl, (5-aryl-1,3-dioxa-cyclopenten-2-one-yl)methyl, -C_{1-10} alkyl-NR^7R^{7a}, $-CH(R^8)OC(=O)R^9$, $-CH(R^8)OC(=O)OR^9$, and



R^7 is selected from H and C_{1-10} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl-, and phenyl-C_{1-6} alkyl-;

R^{7a} is selected from H and C_{1-10} alkyl, C_{2-6} alkenyl, C_{3-6} cycloalkyl-C_{1-3} alkyl-, and phenyl-C_{1-6} alkyl-;

R^8 is selected from H and C_{1-4} linear alkyl;

R^9 is selected from H, C_{1-8} alkyl substituted with 1-2 R^e, C_{3-8} cycloalkyl substituted with 1-2 R^e, and phenyl substituted with 0-2 R^b;

R^e, at each occurrence, is selected from C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{1-5} alkoxy, phenyl substituted with 0-2 R^b;

p, at each occurrence, is selected from 0, 1, and 2;

r, at each occurrence, is selected from 0, 1, 2, 3, 4, and 5;

r', at each occurrence, is selected from 0, 1, 2, 3, 4, and 5;

r", at each occurrence, is selected from 1, 2, and 3;

s, at each occurrence, is selected from 0, 1, 2, and 3; and,

s', at each occurrence, is selected from 0, 1, 2, and 3.

[2] In a preferred embodiment, the present invention provides a novel compound of formula I, wherein;

A is selected from COR^5, $-CO_2H$, CH_2CO_2H, -CONHOH, $-CONHOR^5$, $-CONHOR^6$, $-N(OH)COR^5$, -SH, and $-CH_2SH$;

ring B is a 4-7 membered cyclic amide containing from 0-2 additional heteroatoms selected from O, NR^a, and $S(O)_p$, and 0-1 additional carbonyl groups and 0-1 double bonds;

U is absent;

Y is absent;

Z is absent or selected from a C_{5-10} carbocyclic residue substituted with 0-5 R^b and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^b;

U^a is absent or is selected from: O, NR^a, C(O), $C(O)NR^a$, $NR^aC(O)$, $OC(O)NR^a$, $NR^aC(O)O$, $NR^aC(O)NR^a$, $S(O)_pNR^a$, and $NR^aS(O)_p$;

R^2 is selected from H, Q', C_{1-5} alkylene-Q', C_{2-5} alkenylene-Q', C_{2-5} alkynylene-Q', $(CRR')_r$'$O(CRR')_r$-Q',

$(CRR')_r$-$NR^a(CRR')_r$-Q', $(CRR')_r$-$NR^aC(O)(CRR')_r$-Q', $(CRR')_r$-$C(O)NR^a(CRR')_r$-Q', $(CRR')_r$-$NR^aC(O)NR^a(CRR')_r$-Q', $(CRR')_r$-$C(O)(CRR')_r$-Q', $(CRR')_r$-$C(O)O(CRR')_r$-Q', $(CRR')_r$-$S(O)_p(CRR')_r$-Q', and $(CRR')_r$-$SO_2NR^a(CRR')_r$-Q';

Q' is selected from H, phenyl substituted with 0-3 R^b and a 5-6 membered heteroaryl system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R^b;

R^3 is selected from H, Q, C_{1-10} alkylene-Q, C_{2-10} alkenylene-Q, C_{2-10} alkynylene-Q, $(CRR')_r$-$O(CRR')_r$-Q, $(CRR')_r$-$NR^a(CRR')_r$-Q, $(CRR')_r$-$C(O)(CRR')_r$-Q, $(CRR')_r$-$C(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)(CRR')_r$-Q, $(CRR')_r$-$OC(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)O(CRR')_r$-Q, $(CRR')_r$-$NR^aC(O)NR^a(CRR')_r$-Q, $(CRR')_r$-$S(O)_p(CRR')_r$-Q, $(CRR')_r$-$SO_2NR^a(CRR')_r$-Q, $(CRR')_r$-$NR^aSO_2(CRR')_r$-Q, and $(CRR')_r$-$NR^aSO_2NR^a(CRR')_r$-Q;

R, at each occurrence, is independently selected from H, CH_3, and CH_2CH_3;

R', at each occurrence, is independently selected from H and CH_3;

Q is selected from H, a C_{3-10} carbocyclic residue substituted with 0-5 R^b and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^b; and,

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $S(O)_pR^a$, CF_3, CF_2CF_3, and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S.

[3] In a more preferred embodiment, the present invention provides a novel compound of formula I, wherein;

A is selected from $-CO_2H$, CH_2CO_2H, -CONHOH, $-CONHOR^5$, and $-N(OH)COR^5$;

ring B is a 4-6 membered cyclic amide containing from 0-2 additional heteroatoms selected from O, NR^a, and $S(O)_p$, and 0-1 additional carbonyl groups and 0-1 double bonds;

Z is absent or selected from a C_{5-6} carbocyclic residue substituted with 0-3 R^b and a 5-9 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^b;

U^a is absent or is selected from: O, NR^a, C(O), $C(O)NR^a$, $NR^aC(O)$, and $S(O)_pNR^a$;

X^a is absent or C_{1-10} alkylene;

R^2 is selected from H, C_{1-5} alkylene-Q', $(CH_2)_r O(CH_2)_r$-Q', $(CH_2)_r NR^a(CH_2)_r$-Q', $(CRR')_r NR^aC(O)(CRR')_r$-Q', $(CH_2)_r C(O)NR^a(CH_2)_r$-Q', $(CRR')_r NR^aC(O)NR^a(CRR')_r$-Q', and $(CH_2)_r C(O)(CH_2)_r$-Q';

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $S(O)_pR^a$, CF_3, CF_2CF_3, and a 5-9 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S; and,

Q is selected from H, a C_{5-6} carbocyclic residue substituted with 0-5 R^b and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^b.

[4] In a further preferred embodiment, the present invention provides a novel compound of formula I, wherein;

A is selected from $-CO_2H$, CH_2CO_2H, -CONHOH, and $-CONHOR^5$;

ring B is a 4-5 membered cyclic amide containing from 0-2 additional heteroatoms selected from O, NR^a, and $S(O)_p$, and 0-1 additional carbonyl groups and 0-1 double bonds;

X is absent or selected from C_{1-4} alkylene, C_{2-4} alkenylene, and C_{2-4} alkynylene;

Z is absent or selected from phenyl substituted with 0-3 R^b and a 5-9 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-3 R^b;

X^a is absent or C_{1-4} alkylene;

Y^a is absent or selected from O and NR^a;

Z^a is selected from H, a C_{5-10} carbocyclic residue substituted with 0-5 R^c and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c;

R^4 is selected from H, C_{1-4} alkylene-H, $(CH_2)_r O(CH_2)_r$-H, and $(CH_2)_r NR^a(CH_2)_r$-H; and,

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $S(O)_pR^a$, CF_3, CF_2CF_3, and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S.

[5] In another preferred embodiment, the present invention provides novel compounds selected from:

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-(phenylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-(4-methoxyphenyl)-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-[4-(1-methylethoxy)phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-(1,1-dimethylethoxy)phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-(4-(cyclohexyloxy)phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-[4-(1,1-dimethylethyl)phenylmethoxy]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-(trans-3-phenyl-2-propenyloxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(3-methylphenyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-(2-propenyloxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(3-cyanophenyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α-3-dimethyl-3-[4-[(2-nitrophenyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α-3-dimethyl-3-[4-[(3-nitrophenyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-[4-[(4-nitrophenyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-3-[4-[(1-naphthalenyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-(4-hydroxyphenyl)- α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-2-oxo-3-[4-[(2-pyridinyl)methoxy]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-2-oxo-3-[4-[(3-pyridinyl)methoxy]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-2-oxo-3-[4-[(4-pyridinyl)methoxy]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-3-[4-(2-methylpropyl)phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-2-oxo-3-phenyl-1-pyrrolidineacetamide;

N-hydroxy-2-oxo-3-phenyl-1-pyrrolidineacetamide;

(+/-)-*N*-hydroxy-3-methyl-2-oxo-3-phenyl-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α-methyl-2-oxo-3-phenyl-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-(4-methoxyphenyl)-α-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-cyclohexyl-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-(2-phenylethyl)-1-pyrrolidineacetamide;

[1(*R*)]-3-(2-cyclohexylethyl)-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α-methyl-2-oxo-3-phenyl-3-(phenylmethyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3,4,4',5'-tetrahydro-*N*-hydroxy-α-methyl-2-oxospiro[naphthalene-2(1H),3'-[3H]pyrrole]-1'(2'H)-acetamide;

[1(*R*)]-3-[4-[(3,5-dibromophenyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[[3,5-bis(trifluoromethyl)phenyl]methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(3,5-dichlorophenyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-[4-[(2-methyl-1-naphthalenyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(3,5-dimethoxyphenyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[[4-chloro-2-(trifluoromethyl)-6-quinolinyl]methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-[[4-(1,2,3-thiadiazol-4-yl)phenyl]methoxy]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-([1,1'-biphenyl]-2-ylmethoxy)phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide ;

[1(*R*)]-3-[4-(1*H*-benzotriazol-1-ylmethoxy)phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(4,6-dimethyl-2-pyrimidinyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide ;

[1(*R*)]-3-[4-(1,3-benzodioxol-5-ylmethoxy)phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2-chloro-6-ethoxy-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-(4-quinolinylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(4,5-dimethyl-2-thiazolyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-[4-[(3-methyl-5-nitrophenyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(3-amino-5-methylphenyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[[3-(acetylamino)-5-methylphenyl]methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-1,1-dimethylethyl [2-[[3-[[4-[1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-3-methyl-2-oxo-3-pyrrolidinyl]phenoxy]methyl]-5-methylphenyl]amino]-2-oxoethyl]carbamate;

[1(*R*)]-3-[4-[[3-[(aminoacetyl)amino]-5-methylphenyl]methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-1,1-dimethylethyl [2-[[2-[[3-[[4-[1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-3-methyl-2-oxo-3-pyrrolidinyl]phenoxy]methyl]-5-methylphenyl]amino]-2-oxoethyl]amino]-2-oxoethyl]carbamate;

[1(*R*)]-3-[4-[[3-[[[(aminoacetyl)amino]acetyl]amino]-5-methylphenyl]methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-[3-[[4-[1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-3-methyl-2-oxo-3-pyrrolidinyl]phenoxy]methyl]-5-methylphenyl]-4-morpholinecarboxamide;

3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-α,α,3-trimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[1,1'-biphenyl]-4-yl-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-(2'-methyl[1,1'-biphenyl]-4-yl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-(4'-methyl[1,1'-biphenyl]-4-yl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)-3-(3',4'-dimethoxy[1,1'-biphenyl]-4-yl)-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-2-oxo-3-[2'-(trifluoromethyl)[1,1'-biphenyl]-4-yl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-3-[4-(4-methylphenoxy)phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-2-oxo-3-(4-phenoxyphenyl)-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-3-[4-(2-methylphenoxy)phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-(3,5-dichlorophenoxy)phenyl]-*N*-hydroxy- α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-(3,4-dimethoxyphenoxy)phenyl]-*N*-hydroxy- α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-(1,3-benzodioxol-5-yloxy)phenyl]-*N*-hydroxy- α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-3-[4-[3-(1-methylethyl)phenoxy]phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-[4-(3-methoxyphenoxy)phenyl]- α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-2-oxo-3-[4-(3-thienyloxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-(3,4,5-trimethoxyphenoxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[3,5-bis(trifluoromethyl)phenoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-[4-(1-naphthalenyloxy)phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-[4-[3-[(hydroxyimino)methyl]phenoxy]phenyl]-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-[4-[4-[1-(hydroxyimino)ethyl]phenoxy]phenyl]-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-([1,1'-biphenyl]-4-yloxy)phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-(3,5-dibromophenoxy)phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[3-(acetylamino)phenoxy]phenyl]--hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-[4-(4-nitrophenoxy)phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-(4-methylphenyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[[(2,6-dimethyl-4-pyridinyl)oxy]methyl]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide ;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-[(4-quinolinyloxy)methyl]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-(4-nitrophenyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-[(phenylcarbonyl)amino]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-[(phenylsulfonyl)amino]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-[[(phenylamino)carbonyl]amino]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-[4-[(1-naphthalenylmethyl)amino]phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-[(4-quinolinylmethyl)amino]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[[(3,5-dimethoxyphenyl)methyl]amino]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-methyl-α-(1-methylethyl)-2-oxo-3-[4-(4-quinolinylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-methyl-α-(1-methylethyl)-2-oxo-3-[4-(phenylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-α-(1-methylethyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-α-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-α-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[[3,5-bis(trifluoromethyl)phenyl]methoxy]phenyl]-*N*-hydroxy-3-methyl-α-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(3,5-dichlorophenyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-α-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-methyl-α-(2-methylpropyl)-2-oxo-3-[3-(phenylmethoxy)propyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-methyl-3-[2-methyl-4-(phenylmethoxy)phenyl]-α-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]-2-methylphenyl]-*N*-hydroxy-3-methyl-α-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-methyl-3-[2-methyl-4-(2-naphthalenylmethoxy)phenyl]-α-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-methyl-α-(2-methylpropyl)-3-[2-methyl-4-(4-pyridinylmethoxy)phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]-2-methylphenyl]-*N*-hydroxy-3-methyl-α-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-methyl-α-[2-(methylthio)ethyl]-2-oxo-3-[4-(phenylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-(3,5-dibromophenoxy)phenyl]-3-methyl-α-[2-(methylsulfonyl)ethyl]-2-oxo-1-pyrrolidineacetic acid;

[1(*R*)]-3-[4-[3,5-bis(trifluoromethyl)phenoxy]phenyl]-N-hydroxy-3-methyl-α-[2-(methylsulfonyl)ethyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-(3,5-dibromophenoxy)phenyl]-*N*-hydroxy-3-methyl-α-[2-(methylsulfonyl)ethyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-α-[2-(methylsulfonyl)ethyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-α-[2-(methylsulfonyl)ethyl]-2-oxo-1-pyrrolidineacetamide ;

[1(*R*)]-*N*-hydroxy-3-methyl-α-[2-(methylsulfonyl)ethyl]-2-oxo-3-[4-(4-quinolinylmethoxy)phenyl]-1-pyrrolidineacetamide;

N-hydroxy-1-[3-methyl-2-oxo-3-[4-(phenylmethoxy)phenyl]-1-pyrrolidinyl]cyclopropanecarboxamide;

[1(*R*)]-*N*-hydroxy-α-[(4-hydroxyphenyl)methyl]-3-methyl-2-oxo-3-[4-(phenylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-α-(2-hydroxyethyl)-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-1,1-dimethylethyl [5-[3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-6-(hydroxyamino)-6-oxohexyl]carbamate;

[1(*R*)]-α-(4-aminobutyl)-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-α-[4-(acetylamino)butyl]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-[5-[3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-6-(hydroxyamino)-6-oxohexyl]-3-pyridineacetamide;

[1(*R*)]-*N*-[5-[3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-6-(hydroxyamino)-6-oxohexyl]-4-morpholinecarboxamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-α-[4-[(methylsulfonyl)amino]butyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-α-[4-(acetylamino)butyl]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-1,1-dimethylethyl [5-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-6-(hydroxyamino)-6-oxohexyl]carbamate;

[1(*R*)]-α-(4-aminobutyl)-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-α-[4-[(aminoacetyl)amino]butyl]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-α-[4-(acetylamino)butyl]-3-[4-[[3,5-bis(trifluoromethyl)phenyl]methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-1,1-dimethylethyl [5-[3-[4-(3,5-dibromophenoxy)phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-6-(hydroxyamino)-6-oxohexyl]carbamate;

[1(*R*)]-α-(4-aminobutyl)-3-[4-(3,5-dibromophenoxy)phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-1,1-dimethylethyl [3-[3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-4-(hydroxyamino)-4-oxobutyl]carbamate;

[1(*R*)]-α-(2-aminoethyl)-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-α-[2-(acetylamino)ethyl]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-1,1-dimethylethyl [3-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-4-(hydroxyamino)-4-oxobutyl]carbamate;

[1(*R*)]-α-(2-aminoethyl)-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

N-[3-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-4-(hydroxyamino)-4-oxobutyl]-3-pyridinecarboxamide;

[1(*R*)]-*N*-[3-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-4-(hydroxyamino)-4-oxobutyl]-4-morpholinecarboxamide;

[1(*R*)]-1,1-dimethylethyl [2-[[3-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-4-(hydroxyamino)-4-oxobutyl]amino]-2-oxoethyl]carbamate;

[1(*R*)]-α-[2-[(aminoacetyl)amino]ethyl]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-1,1-dimethylethyl [2-[[2-[[3-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-4-(hydroxyamino)-4-oxobutyl]amino]-2-oxoethyl]amino]-2-oxoethyl]carbamate;

[1(*R*)]-α-[2-[[[(aminoacetyl)amino]acetyl]amino]ethyl]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3-methyl-2-oxo-α-[(phenylmethoxy)methyl]-3-[4-(phenylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-α-(hydroxymethyl)-3-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-1,1-dimethylethyl 4-[2-(hydroxyamino)-1-[3-methyl-2-oxo-3-[4-(4-quinolinylmethoxy)phenyl]-1-pyrrolidinyl]-2-oxoethyl]-1-piperidinecarboxylate;

[1(*R*)]-*N*-hydroxy-α-[3-methyl-2-oxo-3-[4-(4-quinolinylmethoxy)phenyl]-1-pyrrolidinyl]-4-piperidineacetamide;

[1(*R*)]-*N*-hydroxy-α-[3-methyl-2-oxo-3-[4-(4-quinolinylmethoxy)phenyl]-1-pyrrolidinyl]-1-(methylsulfonyl)-4-piperidineacetamide;

[1(*R*)]-1-(2-furanylcarbonyl)-*N*-hydroxy-α-[3-methyl-2-oxo-3-[4-(4-quinolinylmethoxy)phenyl]-1-pyrrolidinyl]-4-piperidineacetamide;

[1(*R*)]-1,1-dimethylethyl 4-[1-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-2-(hydroxyamino)-2-oxoethyl]-1-piperidinecarboxylate;

[1(*R*)]-α-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-4-piperidineacetamide;

[1(*R*)]-methyl 4-[1-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-2-(hydroxyamino)-2-oxoethyl]-1-piperidinecarboxylate;

[1(*R*)]-α-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-1-(methylsulfonyl)-4-piperidineacetamide;

[1(*R*)]-1-acetyl-α-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-4-piperidineacetamide;

[1(*R*)]-1-(2,2-dimethyl-1-oxopropyl)-α-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-4-piperidineacetamide;

[1(*R*)]-α-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-1-methyl-4-piperidineacetamide;

[1(*R*)]-α-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-3-methyl-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-1-(1-methylethyl)-4-piperidineacetamide;

[1(R)]-3-amino-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[4-(2-quinolinylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-N-hydroxy-alpha-methyl-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-3-[[(ethylamino]carbonyl]amino]-N-hydroxy-alpha-methyl-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-N-hydroxy-alpha-methyl-3-[(methylsulfonyl)amino]-2-oxo-1-pyrrolidineacetamide;

[1(R)]-N-[3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-oxo-3-pyrrolidinyl]-3-pyridineacetamide;

[1(R)]-N-[3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-oxo-3-pyrrolidinyl]-4-pyridinecarboxamide;

[1(R)]-3-amino-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-methyl-2-oxo-1-pyrrolidineacetamide;

1(R)]-N-[3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-oxo-3-pyrrolidinyl]-4-pyridinecarboxamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-[[(ethylamino)carbonyl]amino]-N-hydroxy-alpha-methyl-2-oxo-1-pyrrolidineacetamide;

[1(R)]-1,1-dimethylethyl [2-[[3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-oxo-3-pyrrolidinyl]amino]-2-oxoethyl]carbamate;

[1(R)]-3-[(aminoacetyl)amino]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-methyl-2-oxo-1-pyrrolidineacetamide;

[1(R)]-N-[3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-oxo-3-pyrrolidinyl]-3-pyridineacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-methyl-2-oxo-3 [[[(phenylmethyl)amino]carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-[[[(2,4-dimethoxyphenyl)amino]carbonyl]amino]-N-hydroxy-alpha-methyl-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-methyl-2-oxo-3-[[(phenylamino)carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-1,1-dimethylethyl [3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-oxo-3-pyrrolidinyl]carbamate;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-methyl-3-[[[[2-(4-morpholinyl)ethyl]amino]carbonyl]amino]-2-oxo-1-pyrrolidineacetamide;

[1(R)]-1,1-dimethylethyl N-[[[3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-oxo-3-pyrrolidinyl]amino]carbonyl]glycine;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-methyl-2-oxo-3-[[(2-thiazolylamino)carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-methyl-2-oxo-3-[[(4-pyridinylamino)carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-3-[[[(3-hydroxyphenyl)amino]carbonyl]amino]-alpha-methyl-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-3-[[[(2,3-dihydro-2-oxo-1H-benzimidazol-5-yl)amino]carbonyl]amino]-N-hydroxy-alpha-methyl-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-[2-(methylsulfonyl)ethyl]-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-[2-(methylsulfonyl)ethyl]-2-oxo-1-pyrrolidine acetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-[2-(methylsulfonyl)ethyl]-2-oxo-3-[[(2-thiazolylamino)carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-[2-(methylsulfonyl)ethyl]-2-oxo-3-[[(2-thiazolylamino)carbonyl]amino]-1-pyrrolidineacetamide;

[5(R)]-2-propenyl [5-[3-amino-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-6-(hydroxyamino)-6-oxohexyl]carbamate;

[5(R)]-2-propenyl [5-[3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-6-(hydroxyamino)-6-oxohexyl]carbamate;

[1(R)]-3-amino-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[[(2-thiazolylamino)carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[[(2-thiazolylamino)carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[[(2-pyridinylamino)carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[(trifluoroacetyl)amino]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[[(2-pyridinylamino)carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[[[(phenylsulfonyl)amino]carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[[[(phenylsulfonyl)amino]carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-3-[[[(3-methyl-5-isothiazolyl)amino]carbonyl]amino]-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-[[(1H-benzimidazol-2-ylamino)carbonyl]amino]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-[[(1H-benzimidazol-2-ylamino)carbonyl]amino]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[[(phenylamino)carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[[(phenylamino)carbonyl]amino]-1-pyrrolidineacetamide;

[1(R)]-1-[1-[(hydroxyamino)carbonyl]-3-methylbutyl]-N,N,N-trimethyl-2-oxo-3-[4-(phenylmethoxy)phenyl]-1-pyrrolidinemethanaminium;

[1(R)]-3-amino-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[4-(4-quinolinylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(R)]-3-amino-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[4-(2-oxo-2-phenylethoxy)phenyl]-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[(3,5-dimethyl-4-isoxazolyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[2-(2-benzothiazolylamino)-2-oxoethoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-N-hydroxy-3-[4-[(2-methoxy-4-quinolinyl)methoxy]phenyl]-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[4-[(2-phenyl-4-quinolinyl)methoxy]phenyl]-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[(2,6-dimethyl-4-quinolinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[(2-chloro-4-quinolinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[2-(2,5-dimethoxyphenyl)-2-(hydroxyimino)ethoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-N-hydroxy-3-[4-[(2-methylimidazo[1,2-a]pyridin-3-yl)methoxy]phenyl]-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[[1,4-dimethyl-2-(methylthio)-1H-imidazol-5-yl]methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[[1,5-dimethyl-2-(methylthio)-1H-imidazol-4-yl]methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[(2,4-dimethyl-5-thiazolyl)methoxy]phenyl]-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-N-hydroxy-alpha-(2-methylpropyl)-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[(2-chloro-4-quinolinyl)methoxy]phenyl]-N-hydroxy-alpha-[2-(methylsulfonyl)ethyl]-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-N-hydroxy-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-alpha-[2-(methylsulfonyl)ethyl]-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[(3,5-dimethoxyphenyl)methoxy]phenyl]-N-hydroxy-alpha-[2-(methylsulfonyl)ethyl]-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-N-hydroxy-3-[4-[(2-methoxy-4-quinolinyl)methoxy]phenyl]-alpha-[2-(methylsulfonyl)ethyl]-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-amino-3-[4-[(3,5-dimethoxyphenyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-(aminomethyl)-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-(2-methylpropyl)-2-oxo-3-[[[(2-thiazolylamino)carbonyl]amino]methyl]-1-pyrrolidineacetamide;

[1(R)]-3-(aminomethyl)-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-methyl-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-alpha-methyl-2-oxo-3-[[[(2-thiazolylamino)carbonyl]amino]methyl]-1-pyrrolidineacetamide;

[1(R)]-4-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-N-hydroxy-alpha,4-dimethyl-5-oxo-1-imidazolidineacetamide;

[1(R)]-3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-N-hydroxy-3-(hydroxymethyl)-alpha-methyl-2-oxo-1-pyrrolidineacetamide;

[1(R)]-[3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-oxo-3-pyrrolidinyl]methyl ethylcarbamate;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-N-hydroxy-3-(hydroxymethyl)-alpha-methyl-2-oxo-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-N-hydroxy-alpha,3-dimethyl-2-oxo-1-azetidineacetamide;

[1(R)]-3-[5-[(3,5-dimethylphenoxy)methyl]-2-thiazolyl]-N-hydroxy-alpha,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(R)]-4-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-N-hydroxy-alpha-methyl-2,5-dioxo-4-(2-propenyl)-1-imidazolidineacetamide;

[1(R)]-N-hydroxy-alpha,3-dimethyl-2-oxo-3-[[4-(phenylmethoxy)phenyl]methyl]-1-pyrrolidineacetamide;

[1(R)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-N-hydroxy-3-(methylamino)-alpha-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(R)]-N-hydroxy-3-(methylamino)-alpha-(2-methylpropyl)-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(R)]-alpha,3-dimethyl-N-hydroxy-2-oxo-3-[4-(phenylmethoxy)phenyl]-1-piperidineacetamide ;

[1(*R*)]-α-[3-amino-2-oxo-3-[4-(4-quinolinylmethoxy)phenyl]-1-pyrrolidinyl]-*N*-hydroxy-4-piperidineacetamide;

[1(*R*)]-α-[3-amino-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-4-piperidineacetamide;

[1(*R*)]-1,1-dimethylethyl 4-[1-[3-[[(1,1-dimethylethoxy)carbonyl]amino]-3-[4-[(1,1-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-2-(hydroxyamino)-2-oxoethyl]-1-piperidinecarboxylate;

[1(*R*)]-α-[3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-4-piperidineacetamide;

[1(*R*)]-α-[3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-1-(methylsulfonyl)-4-piperidineacetamide;

[1(*R*)]-1-acetyl-α-[3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-4-piperidineacetamide;

[1(*R*)]-α-[3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-1-(2,2-dimethyl-1-oxopropyl)-*N*-hydroxy-4-piperidineacetamide;

[1(*R*)]-1,1-dimethylethyl 4-[1-[3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-2-(hydroxyamino)-2-oxoethyl]-1-piperidinecarboxylate;

[1(*R*)]-methyl 4-[1-[3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-2-(hydroxyamino)-2-oxoethyl]-1-piperidinecarboxylate;

[1(*R*)]-α-[3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-*N*-hydroxy-1-methyl-4-piperidineacetamide;

[1(*R*)]-α-[3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-1-dimethylcarbamyl-*N*-hydroxy-4-piperidineacetamide ;

[1(*R*)]-α-[3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-1-cyclopropanecarbonyl-*N*-hydroxy-4-piperidineacetamide ;

[1(*R*)]-3-amino-*N*-hydroxy-α-(1-methylethyl)-2-oxo-3-[4-(4-quinolinylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-α-(1-methylethyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-amino-α-cyclohexyl-*N*-hydroxy-2-oxo-3-[4-(4-quinolinylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-amino-α-cyclohexyl-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-2-oxo-1-pyrrolidineacetamide;

3-amino-α-(1,1-dimethylethyl)-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-amino-α-(1,1-dimethylethyl)-*N*-hydroxy-2-oxo-3-[4-(4-quinolinylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-amino-α-(1,1-dimethylethyl)-*N*-hydroxy-2-oxo-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-amino-*N*-hydroxy-α-(1-methylethyl)-2-oxo-3-[4-[(2-methyl-4-quinolinyl)methoxy]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-amino-*N*-hydroxy-α-(1-methylethyl)-2-oxo-3-[4-[(2,6-dimethyl-4-quinolinyl)methoxy]phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-*N*-[4-[1-[3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-2-(hydroxyamino)-2-oxoethyl]-1-piperidine]-4-morpholinecarboxamide;

[1(*R*)]-α-[3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-1-pyrrolidinyl]-1-(2-methyl-1-oxopropyl)-*N*-hydroxy-4-piperidineacetamide ;

[1(*R*)]-3-amino-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-α-(4-methoxycyclohexyl)-2-oxo-1-pyrrolidineacetamide;

[1'(*R*)]-*N*-hydroxy-1,2-dihydro-α-(1-methylethyl)-2,2'-dioxo-6-(phenylmethoxy)spiro[3*H*-indole-3,3'-pyrrolidine]-1'-acetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[3-(phenylmethoxy)phenyl]-1-pyrrolidineacetamide;

[1(*R*)]-3-[3-[(3,5-dimethylphenyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-[3-[(3-methylphenyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-[3-(1-methylethoxy)phenyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[3-(heptyloxy)phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-α1-methyl-2-oxo-*N*3-1,3,4-thiadiazol-2-yl-1,3-pyrrolidinediacetamide;

[1(*R*)]-1,1-dimethylethyl 1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-oxo-3-[4-(phenylmethoxy)phenyl]-3-pyrrolidineacetate;

[1(*R*)]-1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-oxo-3-[4-(phenylmethoxy)phenyl]-3-pyrrolidineacetic acid;

[1(*R*)]-3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-*N*1-hydroxy-α1-methyl-*N*3-[2-(methylamino)-2-oxoethyl]-2-oxo-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-*N*1-hydroxy-α1-methyl-2-oxo-*N*3-2-thiazolyl-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-*N*-hydroxy-α-methyl-3-[2-(4-morpholinyl)-2-oxoethyl]-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-α1-methyl-2-oxo-*N*3-2-thiazolyl-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-α1-methyl-2-oxo-*N*3-[2-(4-morpholinyl)ethyl]-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-α1-methyl-2-oxo-*N*3-(4-pyridinylmethyl)-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy- α1-methyl-2-oxo-*N*3-2-thiazolyl-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy- α1-methyl-2-oxo-*N*3-(3-pyridinylmethyl)-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy- α1-methyl-2-oxo-*N*3-(2-pyridinylmethyl)-1,3-pyrrolidinediacetamide;

[1(R)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy- α1-methyl-2-oxo-*N*3-4-pyridinyl-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy- α1-methyl-*N*3-(3-methyl-5-isothiazolyl)-2-oxo-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*3-[5-(1,1-dimethylethyl)-1,3,4-thiadizol-2-yl]-*N*1-hydroxy-α1-methyl-2-oxo-1,3-pyrrolidinediacetamide;

[1(*R*)]-1,1-dimethylethyl 2-[[[3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-oxo-3-pyrrolidinyl]acetyl]amino]-4-thiazoleacetate;

[1(*R*)]-2-[[[3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-1-[2-(hydroxyamino)-1-methyl-2-oxoethyl]-2-oxo-3-pyrrolidinyl]acetyl]amino]-4-thiazoleacetic acid;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-α1-methyl-*N*3-[4-[2-(methylamino)-2-oxoethyl]-2-thiazolyl]-2-oxo-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-(1*H*-benzimidazol-2-ylmethyl)-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-α-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*-hydroxy-3-(3*H*-imidazo(4,5-*c*]pyridin-2-ylmethyl)-α-methyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[3,5-bis(trifluoromethyl)phenoxy]phenyl]-*N*1-hydroxy-α1-methyl-2-oxo-*N*3-2-thiazolyl-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[3,5-bis(trifluoromethyl)phenoxy]phenyl]-*N*1-hydroxy-α1-methyl-2-oxo-*N*3-(4-pyridinylmethyl)-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-α1-(1-methylethyl)-2-oxo-*N*3-(4-pyridinylmethyl)-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-α1-(1-methylethyl)-2-oxo-*N*3-(4-pyridinylmethyl)-1,3-pyrrolidinediacetamide;

[1(*R*)]-α1-(cyclohexylmethyl)-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-2-oxo-*N*3-(4-pyridinylmethyl)-1,3-pyrrolidinediacetamide;

[1(*R*)]-α1-(cyclohexylmethyl)-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-2-oxo-*N*3-(4-pyridinylmethyl)-1,3-pyrrolidinediacetamide;

[1(*R*)]-1,1-dimethylethyl [5-[3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-2-oxo-3-[2-oxo-2-[(4-pyridinylmethyl)amino]ethyl]-1-pyrrolidinyl]-6-(hydroxyamino)-6-oxohexyl]carbamate;

[1(*R*)]-α1-(4-aminobutyl)-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-2-oxo-*N*3-(4-pyridinylmethyl)-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[3-(1*H*-benzotriazol-1-ylmethoxy)phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-*N*-hydroxy-3,4,4-trimethyl-α-[3-methyl-2-oxo-3[4-(phenylmethoxy)phenyl]-1-pyrrolidinyl]-2,5-dioxo-1-imidazolidinepropanamide ;

[1(*R*)]-1,1-dimethylethyl 1-[(hydroxyamino)carbonyl]-3-methylbutyl]-2-oxo-3-[4-(phenyl]-3-pyrrolidineacetate;

[1(*R*)-*N*1-hydroxy-3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-N3-[2-(methylamino)-2-oxoethyl]-α-(2-methylpropyl)-2-oxo-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-*N*3- [2-(methylamino)-2-oxoethyl]-alpha1-(2-methylpropyl)-2-oxo- 1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-α1-(2-methylpropyl)-2-oxo-*N*3-2-thiazolyl-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[3,5-bis(trifluoromethyl)phenoxy]phenyl]-*N*1-hydroxy-*N*3-[2-(methylamino)-2-oxoethyl]-α1-(2-methylpropyl)-2-oxo-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[3,5-bis(trifluoromethyl)phenoxy]phenyl]-*N*1-hydroxy-α1-(2-methylpropyl)-2-oxo-*N*3-(4-pyridinylmethyl)-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dichloro-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-α1-(2-methylpropyl)-2-oxo-*N*3-phenyl-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-*N*3-methyl-α1-(2-methylpropyl)-2-oxo-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-*N*3-[2-(1*H*-imidazol-4-yl)ethyl]-α1-(2-methylpropyl)-2-oxo-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-α1-(2-methylpropyl)-2-oxo-*N*3-[1-(phenylmethyl)-4-piperidinyl]-1,3-pyrrolidinediacetamide;

[1(*R*)]-*N*3-[2-(dimethylamino)ethyl]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-α1-(2-methylpropyl)-2-oxo-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-*N*3-(4-hydroxyphenyl)-α1-(2-methylpropyl)-2-oxo-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*3-hydroxy-α1-(2-methylpropyl)-2-oxo-*N*3-2-thiazolyl-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*3-hydroxy-3-(2-hydroxyethyl)-α1-(2-methylpropyl)-2-oxo-1-pyrrolidineacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*3-(4,5-dimethyl-2-thiazolyl)-*N*1-hydroxy-α1-(2-methylpropyl)-2-oxo-1,3-pyrrolidinediacetamide;

[1(*R*)]-3-[4-[(2,6-dimethyl-4-pyridinyl)methoxy]phenyl]-*N*1-hydroxy-*N*3-*1*H-indazol-5-yl-α1-(2-methylpropyl)-2-oxo-1,3-pyrrolidinediacetamide; and,

[1(*R*)]-3-[4-[3,5-bis(trifluoromethyl)phenoxy]phenyl]-*N*1-hydroxy-α1-(2-methylpropyl)-2-oxo-*N*3-2-thiazolyl-1,3-pyrrolidinediacetamide;

or a pharmaceutically acceptable salt form thereof.

[6] In another preferred embodiment, the present invention provides a novel compound of formula I, wherein:

A is selected from COR^5, $-CO_2H$, CH_2CO_2H, -CONHOH, $-CONHOR^5$, $-CONHOR^6$, $-N(OH)COR^5$, -SH, and $-CH_2SH$;

ring B is a 4-7 membered cyclic amide containing from 0-3 additional heteroatoms selected from O, NR^a, and $S(O)_p$, and 0-1 additional carbonyl groups and 0-1 double bonds;

R^1 and R^2 combine to form a C_{5-14} carbocyclic residue substituted with $R^{1'}$ and 0-3 R^b or a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with $R^{1'}$ and 0-3 R^b;

Z^a is selected from H, a C_{5-10} carbocyclic residue substituted with 0-5 R^c and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c;

R^3 is selected from H, Q, C_{1-10} alkylene-Q, C_{2-10} alkenylene-Q, C_{2-10} alkynylene-Q, $(CRR')_r O(CRR')_r$-Q, $(CRR')_r NR^a(CRR')_r$-Q, $(CRR')_r C(O)(CRR')_r$-Q, $(CRR')_r C(O)NR^a(CRR')_r$-Q, $(CRR')_r NR^a C(O)(CRR')_r$-Q, $(CRR')_r OC(O)NR^a(CRR')_r$-Q, $(CRR')_r NR^a C(O)O(CRR')_r$-Q, $(CRR')_r NR^a C(O)NR^a(CRR')_r$-Q, $(CRR')_r S(O)_p(CRR')_r$-Q, $(CRR')_r SO_2NR^a(CRR')_r$-Q, $(CRR')_r NR^a SO_2(CRR')_r$-Q, and $(CRR')_r NR^a SO_2NR^a(CRR')_r$-Q;

R, at each occurrence, is independently selected from H, CH_3, CH_2CH_3, $CH{=}CH_2$, $CH{=}CHCH_3$, and $CH_2CH{=}CH_2$;

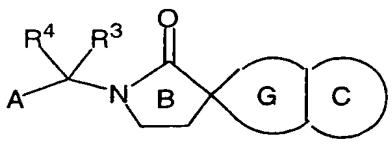
R', at each occurrence, is independently selected from H, CH_3, CH_2CH_3, and $CH(CH_3)_2$;

Q is selected from H, a C_{3-10} carbocyclic residue substituted with 0-5 R^b and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^b;

R^4 is selected from H;

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $S(O)_pR^a$, CF_3, CF_2CF_3, and a 5-10 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S.

[7] In another more preferred embodiment, the present invention provides a novel compound of formula II, wherein:



II

A is selected from $-CO_2H$, CH_2CO_2H, -CONHOH, and $-CONHOR^5$;

ring C is fused to ring G and is a phenyl ring or 5-6 membered aromatic heterocycle containing from 0-4 heteroatoms selected from O, N, and $S(O)_p$, and ring C is substituted with 1 $R^{1'}$;

ring G is a 4-8 membered carbocylic ring substituted with 0-1 carbonyl groups

alternatively, ring G is a 4-8 membered heterocyclic ring containing from 1-2 heteroatoms selected from O and NR^a and subsituted with 0-2 carbonyl groups and 0-1 double bonds;

U^a is absent or is selected from: O, NR^a, C(O), $C(O)NR^a$, $NR^aC(O)$, and $S(O)_pNR^a$;

X^a is absent or C_{1-4} alkylene;

Y^a is absent or selected from O and NR^a;

Z^a is selected from H, phenyl substituted with 0-5 R^c and a 5-9 membered aromatic heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^c;

Q is selected from H, a C_{5-6} carbocyclic residue substituted with 0-5 R^b and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S and substituted with 0-5 R^b; and,

R^c, at each occurrence, is independently selected from C_{1-6} alkyl, OR^a, Cl, F, Br, I, =O, CN, NO_2, $NR^aR^{a'}$, $C(O)R^a$, $C(O)OR^a$, $C(O)NR^aR^{a'}$, $S(O)_2NR^aR^{a'}$, $S(O)_pR^a$, CF_3, CF_2CF_3, and a 5-6 membered heterocyclic system containing from 1-4 heteroatoms selected from the group consisting of N, O, and S.

In a third embodiment, the present invention provides a novel pharmaceutical composition, comprising: a pharmaceutically acceptable carrier and a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In a fourth embodiment, the present invention provides a novel method for treating or preventing an inflammatory disorder, comprising: administering to a patient in need thereof a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In a fifth embodiment, the present invention provides a novel method of treating a condition or disease mediated by MMPs, TNF, aggrecanase, or a combination thereof in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In a sixth embodiment, the present invention provides a novel method of treating a condition or disease wherein the disease or condition is referred to as rheumatoid arthritis, osteoarthritis, periodontitis, gingivitis, corneal ulceration, solid tumor growth and tumor invasion by secondary metastases, neovascular glaucoma, multiple sclerosis, or psoriasis in a mammal, comprising: administering to the mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

In a seventh embodiment, the present invention provides a novel method of treating a condition or disease wherein the disease or condition is referred to as fever, cardiovascular effects, hemorrhage, coagulation, cachexia, anorexia,

alcoholism, acute phase response, acute infection, shock, graft versus host reaction, autoimmune disease or HIV infection in a mammal comprising administering to the mammal in need of such treatment a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt form thereof.

DEFINITIONS

The compounds herein described may have asymmetric centers. Compounds of the present invention containing an asymmetrically substituted atom may be isolated in optically active or racemic forms. It is well known in the art how to prepare optically active forms, such as by resolution of racemic forms or by synthesis from optically active starting materials. Many geometric isomers of olefins, C=N double bonds, and the like can also be present in the compounds described herein, and all such stable isomers are contemplated in the present invention. Cis and trans geometric isomers of the compounds of the present invention are described and may be isolated as a mixture of isomers or as separated isomeric forms. All chiral, diastereomeric, racemic forms and all geometric isomeric forms of a structure are intended, unless the specific stereochemistry or isomeric form is specifically indicated.

The term "substituted," as used herein, means that any one or more hydrogens on the designated atom is replaced with a selection from the indicated group, provided that the designated atom's normal valency is not exceeded, and that the substitution results in a stable compound. When a substituent is keto (i.e., =O), then 2 hydrogens on the atom are replaced. When a ring system (e.g., carbocyclic or heterocyclic) is said to be substituted with a carbonyl group or a double bond, it is intended that the carbonyl group or double bond be part (i.e., within) of the ring.

When any variable (e.g., R^b) occurs more than one time in any constituent or formula for a compound, its definition at each occurrence is independent of its definition at every other occurrence. Thus, for example, if a group is shown to

be substituted with 0-2 R^6, then said group may optionally be substituted with up to two R^6 groups and R^6 at each occurrence is selected independently from the definition of R^6. Also, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

When a bond to a substituent is shown to cross a bond connecting two atoms in a ring, then such substituent may be bonded to any atom on the ring. When a substituent is listed without indicating the atom via which such substituent is bonded to the rest of the compound of a given formula, then such substituent may be bonded via any atom in such substituent. Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms. Examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl, t-butyl, n-pentyl, and s-pentyl. "Haloalkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms, substituted with 1 or more halogen (for example $-C_vF_w$ where v = 1 to 3 and w = 1 to (2v+1)). Examples of haloalkyl include, but are not limited to, trifluoromethyl, trichloromethyl, pentafluoroethyl, and pentachloroethyl. "Alkoxy" represents an alkyl group as defined above with the indicated number of carbon atoms attached through an oxygen bridge. Examples of alkoxy include, but are not limited to, methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy, t-butoxy, n-pentoxy, and s-pentoxy. "Cycloalkyl" is intended to include saturated ring groups, such as cyclopropyl, cyclobutyl, or cyclopentyl. Alkenyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more unsaturated carbon-carbon bonds which may occur in any stable point along the chain, such as ethenyl and propenyl. "Alkynyl" is intended to include hydrocarbon chains of either a straight or branched configuration and one or more triple carbon-carbon

bonds which may occur in any stable point along the chain, such as ethynyl and propynyl.

"Halo" or "halogen" as used herein refers to fluoro, chloro, bromo, and iodo; and "counterion" is used to represent a small, negatively charged species such as chloride, bromide, hydroxide, acetate, sulfate, and the like.

As used herein, "carbocycle" or "carbocyclic residue" is intended to mean any stable 3- to 7-membered monocyclic or bicyclic or 7- to 13-membered bicyclic or tricyclic, any of which may be saturated, partially unsaturated, or aromatic. Examples of such carbocycles include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, adamantyl, cyclooctyl, [3.3.0]bicyclooctane, [4.3.0]bicyclononane, [4.4.0]bicyclodecane (decalin), [2.2.2]bicyclooctane, fluorenyl, phenyl, naphthyl, indanyl, adamantyl, or tetrahydronaphthyl (tetralin).

As used herein, the term "heterocycle" or "heterocyclic system" is intended to mean a stable 5- to 7- membered monocyclic or bicyclic or 7- to 14-membered bicyclic heterocyclic ring which is saturated partially unsaturated or unsaturated (aromatic), and which consists of carbon atoms and from 1 to 4 heteroatoms independently selected from the group consisting of N, O and S and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The nitrogen and sulfur heteroatoms may optionally be oxidized. The heterocyclic ring may be attached to its pendant group at any heteroatom or carbon atom which results in a stable structure. The heterocyclic rings described herein may be substituted on carbon or on a nitrogen atom if the resulting compound is stable. If specifically noted, a nitrogen in the heterocycle may optionally be quaternized. It is preferred that when the total number of S and O atoms in the heterocycle exceeds 1, then these heteroatoms are not adjacent to one another. It is preferred that the total number of S and O atoms in the heterocycle is not more than 1. As used herein, the term "aromatic heterocyclic system" is intended to mean a stable 5- to 7-membered monocyclic or bicyclic or 7- to 14-membered bicyclic

heterocyclic aromatic ring which consists of carbon atoms and from 1 to 4 heterotams independently selected from the group consisting of N, O and S. It is preferred that the total number of S and O atoms in the aromatic heterocycle is not more than 1.

Examples of heterocycles include, but are not limited to, acridinyl, azocinyl, benzimidazolyl, benzofuranyl, benzothiofuranyl, benzothiophenyl, benzoxazolyl, benzthiazolyl, benztriazolyl, benztetrazolyl, benzisoxazolyl, benzisothiazolyl, benzimidazolinyl, carbazolyl, 4a*H*-carbazolyl, carbolinyl, chromanyl, chromenyl, cinnolinyl, decahydroquinolinyl, 2*H*,6*H*-1,5,2-dithiazinyl, dihydrofuro[2,3-*b*]tetrahydrofuran, furanyl, furazanyl, imidazolidinyl, imidazolinyl, imidazolyl, 1*H*-indazolyl, indolenyl, indolinyl, indolizinyl, indolyl, 3H-indolyl, isobenzofuranyl, isochromanyl, isoindazolyl, isoindolinyl, isoindolyl, isoquinolinyl, isothiazolyl, isoxazolyl, methylenedioxyphenyl, morpholinyl, naphthyridinyl, octahydroisoquinolinyl, oxadiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, phenoxathiinyl, phenoxazinyl, phthalazinyl, piperazinyl, piperidinyl, pteridinyl, purinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazole, pyridoimidazole, pyridothiazole, pyridinyl, pyridyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, 2H-pyrrolyl, pyrrolyl, quinazolinyl, quinolinyl, 4*H*-quinolizinyl, quinoxalinyl, quinuclidinyl, tetrahydrofuranyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, 6*H*-1,2,5-thiadiazinyl, 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,3,4-thiadiazolyl, thianthrenyl, thiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiophenyl, triazinyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,5-triazolyl, 1,3,4-triazolyl, and xanthenyl. Preferred heterocycles include, but are not limited to, pyridinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, pyrrolidinyl, imidazolyl, indolyl, benzimidazolyl, 1*H*-indazolyl,

oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, and isatinoyl. Also included are fused ring and spiro compounds containing, for example, the above heterocycles.

The term "amino acid" as used herein means an organic compound containing both a basic amino group and an acidic carboxyl group. Included within this term are natural amino acids (e.g., L-amino acids), modified and unusual amino acids (e.g., D-amino acids), as well as amino acids which are known to occur biologically in free or combined form but usually do not occur in proteins. Included within this term are modified and unusual amino acids,such as those disclosed in, for example, Roberts and Vellaccio (1983) The Peptides, 5: 342-429, the teaching of which is hereby incorporated by reference. Natural protein occurring amino acids include, but are not limited to, alanine, arginine, asparagine, aspartic acid, cysteine, glutamic acid, glutamine, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, serine, threonine, tyrosine, tyrosine, tryptophan, proline, and valine. Natural non-protein amino acids include, but are not limited to arginosuccinic acid, citrulline, cysteine sulfinic acid, 3,4-dihydroxyphenylalanine, homocysteine, homoserine, ornithine, 3-monoiodotyrosine, 3,5-diiodotryosine, 3,5,5'-triiodothyronine, and 3,3',5,5'-tetraiodothyronine. Modified or unusual amino acids which can be used to practice the invention include, but are not limited to, D-amino acids, hydroxylysine, 4-hydroxyproline, an N-Cbz-protected amino acid, 2,4-diaminobutyric acid, homoarginine, norleucine, N-methylaminobutyric acid, naphthylalanine, phenylglycine, ß-phenylproline, tert-leucine, 4-aminocyclohexylalanine, N-methyl-norleucine, 3,4-dehydroproline, N,N-dimethylaminoglycine, N-methylaminoglycine, 4-aminopiperidine-4-carboxylic acid, 6-aminocaproic acid, trans-4-(aminomethyl)-cyclohexanecarboxylic acid, 2-, 3-, and 4-(aminomethyl)-benzoic acid, 1-aminocyclopentanecarboxylic acid, 1-aminocyclopropanecarboxylic acid, and 2-benzyl-5-aminopentanoic acid.

The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

As used herein, "pharmaceutically acceptable salts" refer to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of pharmaceutically acceptable salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The pharmaceutically acceptable salts include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, and the like.

The pharmaceutically acceptable salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, or in a mixture of the two; generally, nonaqueous media like ether, ethyl acetate, ethanol, isopropanol, or acetonitrile are preferred. Lists of suitable salts are found in *Remington's Pharmaceutical*

Sciences, 17th ed., Mack Publishing Company, Easton, PA, 1985, p. 1418, the disclosure of which is hereby incorporated by reference.

Since prodrugs are known to enhance numerous desirable qualities of pharmaceuticals (e.g., solubility, bioavailability, manufacturing, etc...) the compounds of the present invention may be delivered in prodrug form. Thus, the present invention is intended to cover prodrugs of the presently claimed compounds, methods of delivering the same and compositions containing the same. "Prodrugs" are intended to include any covalently bonded carriers which release an active parent drug of the present invention *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs the present invention are prepared by modifying functional groups present in the compound in such a way that the modifications are cleaved, either in routine manipulation or *in vivo*, to the parent compound. Prodrugs include compounds of the present invention wherein a hydroxy, amino, or sulfhydryl group is bonded to any group that, when the prodrug of the present invention is administered to a mammalian subject, it cleaves to form a free hydroxyl, free amino, or free sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to, acetate, formate and benzoate derivatives of alcohol and amine functional groups in the compounds of the present invention.

"Stable compound" and "stable structure" are meant to indicate a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious therapeutic agent.

SYNTHESIS

The compounds of the present invention can be prepared in a number of ways well known to one skilled in the art of organic synthesis. The compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those

skilled in the art. Preferred methods include, but are not limited to, those described below. All references cited herein are hereby incorporated in their entirety herein by reference.

The novel compounds of this invention may be prepared using the reactions and techniques described in this section. The reactions are performed in solvents appropriate to the reagents and materials employed and are suitable for the transformations being effected. Also, in the description of the synthetic methods described below, it is to be understood that all proposed reaction conditions, including choice of solvent, reaction atmosphere, reaction temperature, duration of the experiment and workup procedures, are chosen to be the conditions standard for that reaction, which should be readily recognized by one skilled in the art. It is understood by one skilled in the art of organic synthesis that the functionality present on various portions of the molecule must be compatible with the reagents and reactions proposed. Such restrictions to the substituents which are compatible with the reaction conditions will be readily apparent to one skilled in the art and alternate methods must then be used.

A series of γ-lactams of formula **10** are prepared by the method outlined in Scheme 1 and 2. R^1-substituted methyl acetate **1** is deprotonated to form enolate using bases such as sodium bis(trimethylsilyl)amide, lithium N,N-diisopropylamide, and sodium hydride. Alkylation with R^2-X provides **2**. Further alkylation with allyl bromide under similar basic conditions gives ester **3**. The olefin in **3** is then cleaved by ozonolysis or by dihydroxylation (OsO_4/NMO) followed by diol cleavage (NaIO4) to give aldehyde **4**. Treatment of the aldehyde **4** and D-amino acid **5** with zinc in acetic acid at elevated temperature leads to reductive amination and lactamization to give γ-lactam **7**. The γ-lactamization gives a mixture of two diastereomers epimeric at the quaternary center. The diastereomers of **7** are either separated or taken to the next step as a mixture.

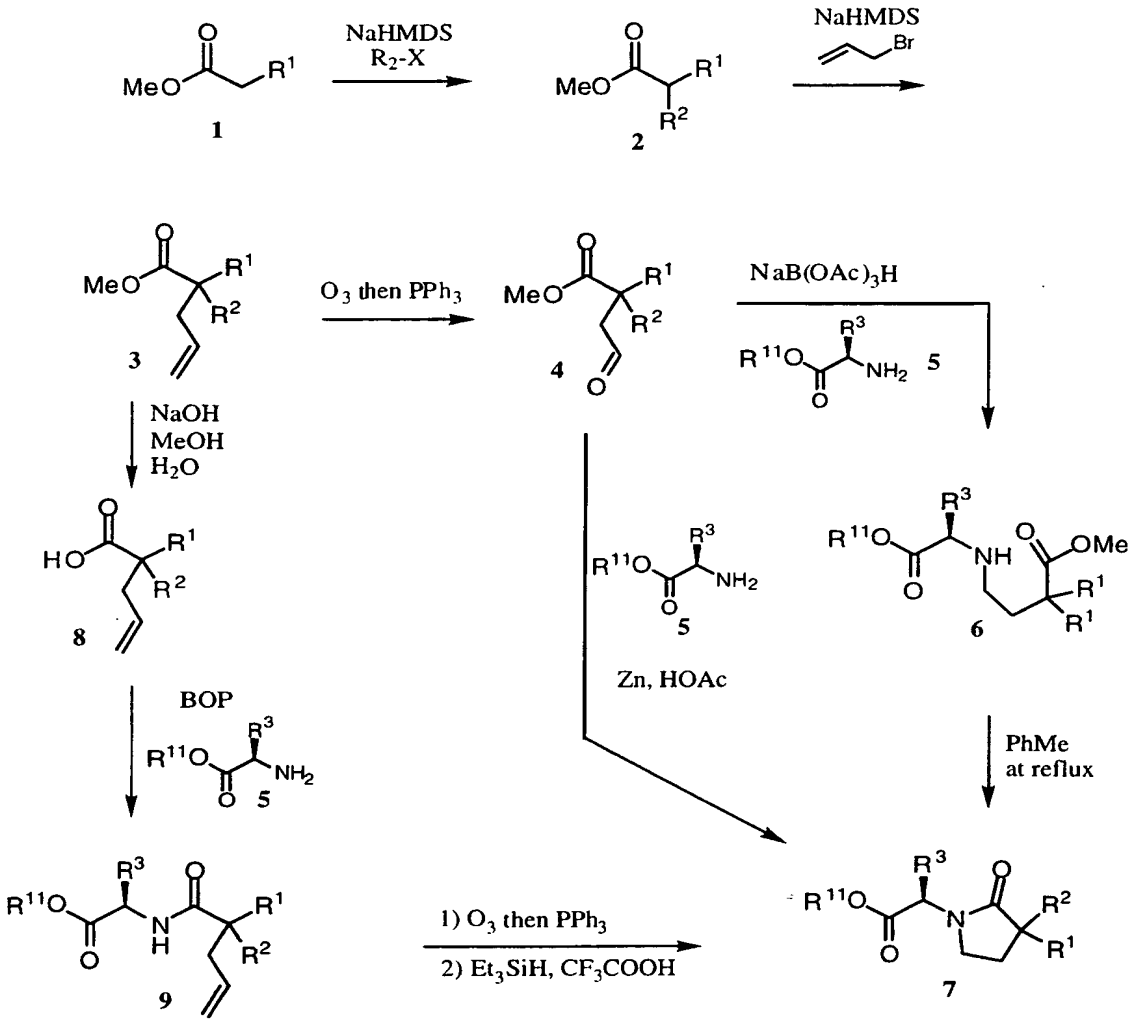
Alternatively, aldehyde **4** is converted to lactam **7** through a stepwise sequence. Condensation of **4** with amino

ester **5** through reductive amination provides secondary amine **6**. The reductive amination can be affected with reagents such as sodium borohydride, sodium cyanoborohydride, and sodium triacetoxyborohydride. Amine **6** is converted to **7** via thermally induced lactamization or methyl ester hydrolysis followed by amide bond formation using reagents such as BOP.

Lactam **7** can also be prepared from ester **3** through the carboxylic acid **8**. Acid **8** and amino ester **5** can be coupled using standard peptide coupling reagents well known in the literature such as DCC, BOP, and TBTU (Bodanszky, M. in Peptide Chemistry A Practical Textbook, 2nd ed. Springer-Verlag, New York, 1993). Olefin degradation (O_3/PPh_3, or $OsO_4/NaIO_4$) and deoxygenation (Et_3SiH/CF_3COOH) gives lactam **7**.

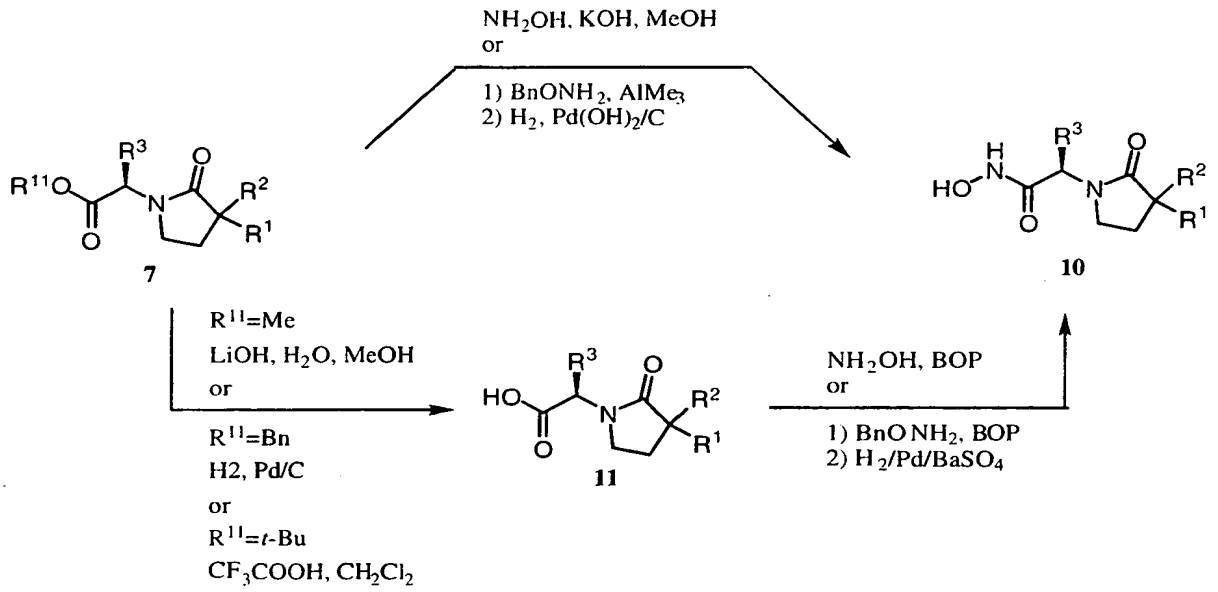
Many of the D-amino acid derivatives **5** are commercially available or are prepared from the commercial material by simple protecting group manipulations. Others are synthesized from glycine using Myers method (Myers, A. G.; Gleason, J. L.; Yoon, T. *J. Am. Chem. Soc.* **1995**, *117*, 8488), from serine using Mitsunobu reactions (Cherney, R. J.; Wang, L. *J. Org. Chem.* **1996**, *61*, 2544), or using Evans electrophilic azidations (Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011).

Scheme 1



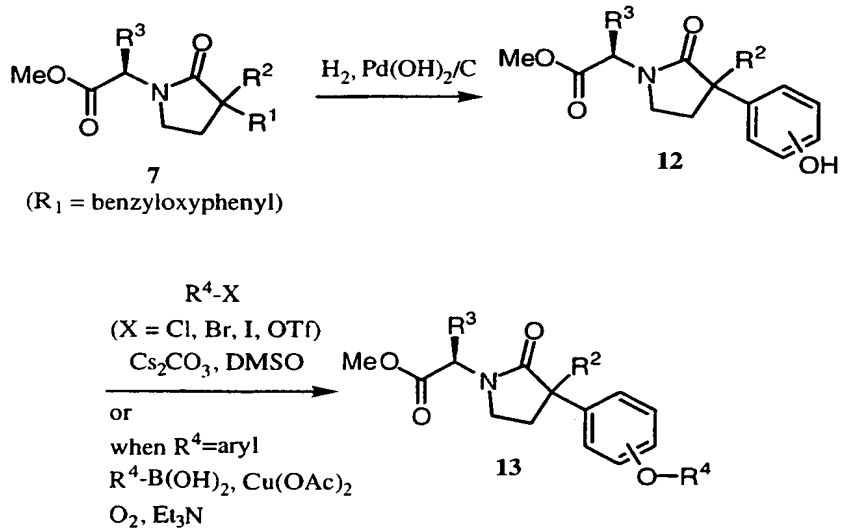
The methyl ester of **7** (R^{11}=Me) is converted to hydroxamic acid **10** by treatment with hydroxylamine under basic conditions (KOH or NaOMe) in methanol (Scheme 2). The methyl ester **7** (R^{11}=Me) can also be converted to benzyl protected hydroxamic acid with O-benzylhydroxylamine using Weinreb's trimethylalluminum conditions (Levin, J. I.; Turos, E.; Weinreb, S. M. *Syn. Commun.* **1982**, *12*, 989) or Roskamp's bis[bis(trimethylsilyl)amido]tin reagent (Wang, W.-B.; Roskamp, E. J. *J. Org. Chem.* **1992**, *57*, 6101). Hydrogenolysis then provides the hydroxamic acid **10**. Alternatively, **10** can be prepared through the carboxylic intermediate **11**. Carboxylic acid **11** is converted to **10** via coupling with hydroxylamine or NH2OBn followed by deprotection.

Scheme 2



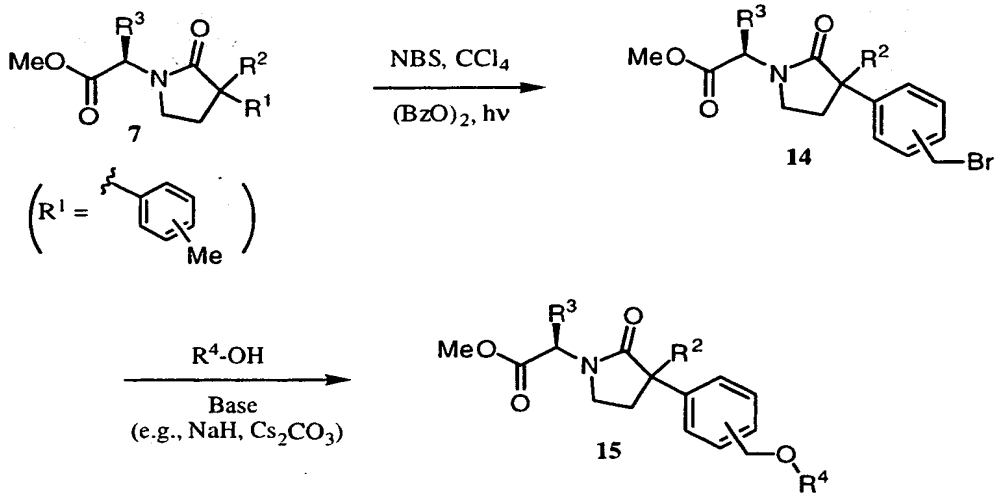
A variety of ethers of 4-hydroxyphenyllactam **13** are prepared using intermediate **7** when R^1 is benzyloxyphenyl group (Scheme 3). Removal of benzyl protecting group followed by alkylation with R^4-X produces **13**. The alkylation can be affected with bases such as K_2CO_3, Cs_2CO_3, NaH, and t-BuOK. Ester **13** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

Scheme 3



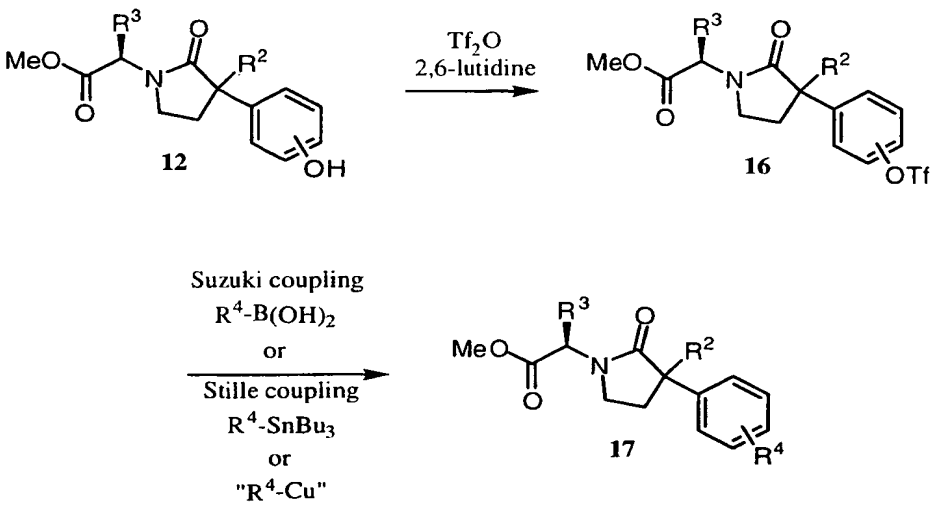
Another series of phenyllactams of formula **15** is prepared following the sequence outlined in Scheme 4. Starting from **7** when R^1 methyl group, radical bromonation with N-bromosuccinimide gives bromide **14**. Alkylation of **14** with R-OH under basic conditions gives **15**. Ester **15** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

Scheme 4



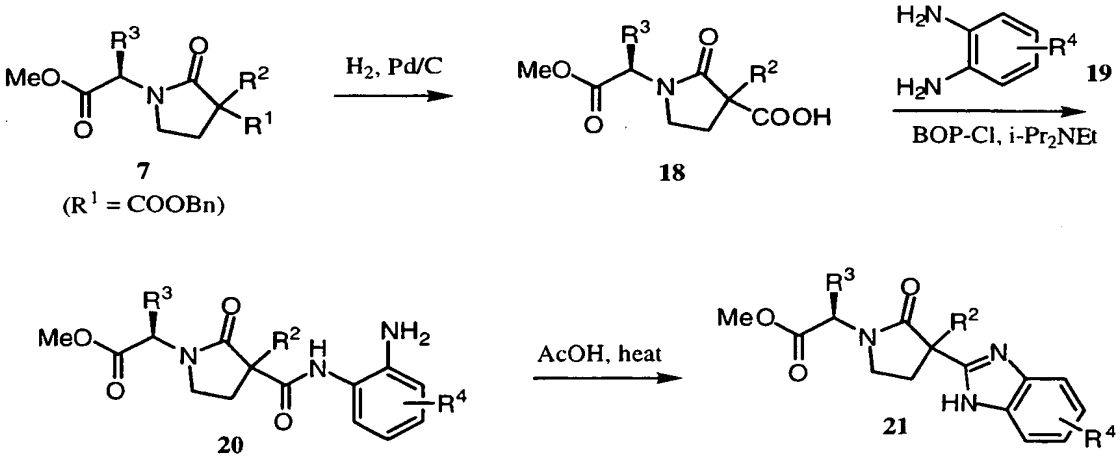
Another series of phenyllactams of formula **17** is prepared following the sequence outlined in Scheme 5. Reaction of **12** with triflic anhydride provides triflate **16**. Palladium-mediated coupling of **16** under Stille or Suzuki conditions provides **17**. Alternatively, **16** reacts with lower or higher-order cuprates to give **17**. Ester **17** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

Scheme 5



A variety of heterocyclic substituted lactams are prepared from **7** when R^1 is carbobenzyloxy group. As a representative example, scheme 6 illustrates the synthesis of the benzimidazole series. Following hydrogenolysis of **7**, the resultant acid **18** is coupled with diamine **19** with coupling reagents such as BOP-Cl. Upon heating of **20** in acetic acid, benzimidazole **21** is formed. Ester **21** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

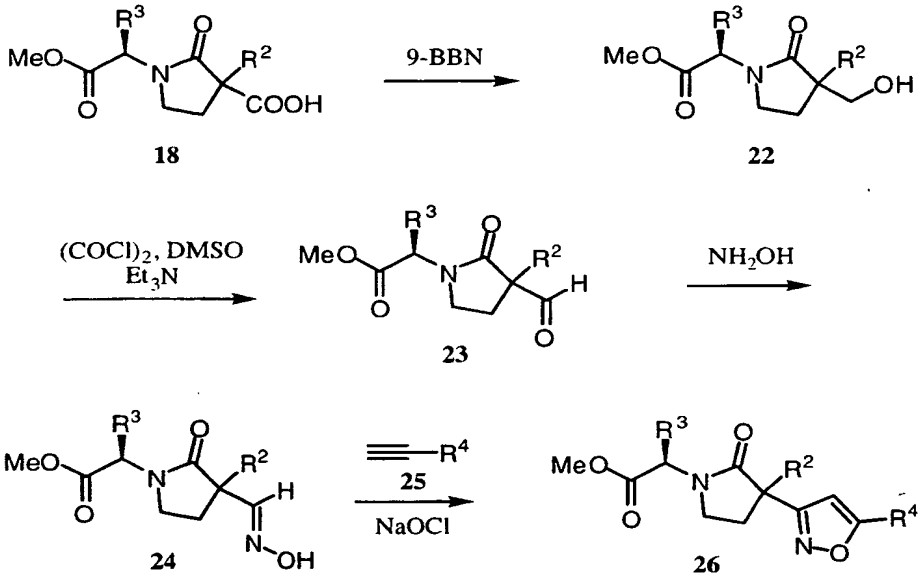
Scheme 6



A series of isoxazole-substituted lactams of formula **26** is prepared using common intermediate **18** following the sequence outlined in Scheme 7. The carboxylic acid **18** is

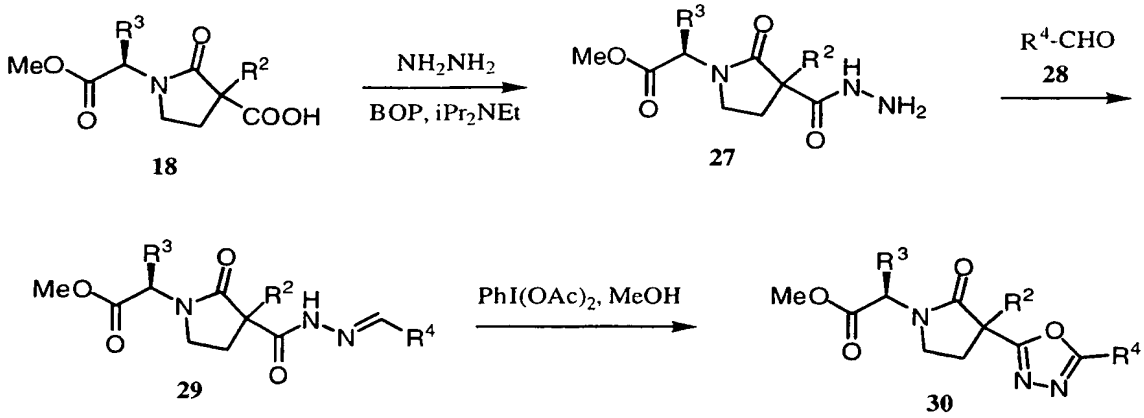
converted to aldehyde **23** by hydroboration and Swern oxidation. Oxime formation, in situ oxidation and [3+2] dipolar cycloaddition with acetylene **25** provides isoxazole **26**. Ester **26** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

Scheme 7



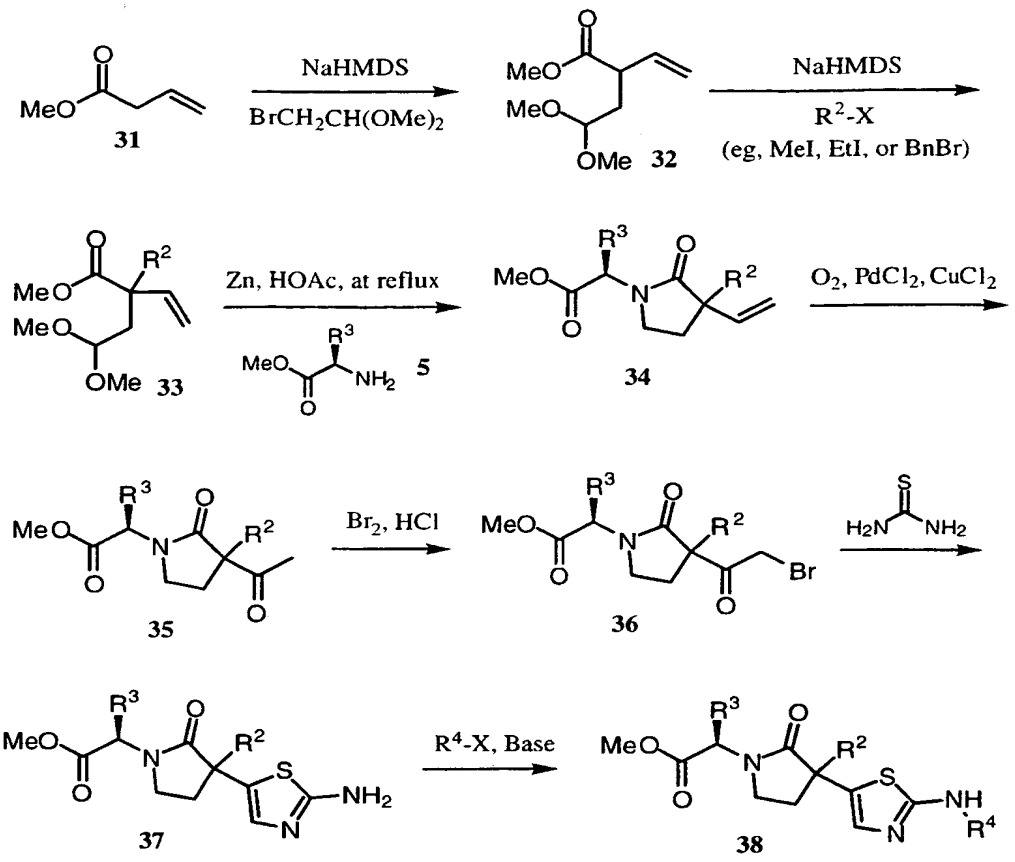
Another series of lactams of formula **30** with an oxadiazole substituent at the α position is prepared using common intermediate **18** following the sequence outlined in Scheme 8. Acid **18** is first coupled with hydrazine to give **27**. Condensation with aldehyde **28** and oxidative cyclization with $PhI(OAc)_2$ provided oxadiazole **30** (Yang, R. Y.; Dai, L. X. *J. Org. Chem.* **1993**, *58*, 3381). Ester **30** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

Scheme 8



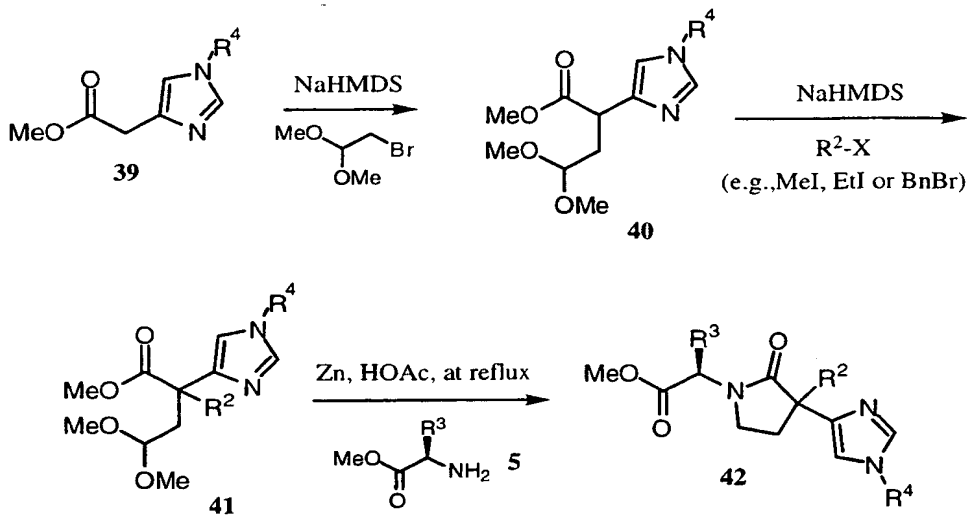
Another series of lactams of formula **38** with an aminothiazole substituent at the α position is prepared following the sequence outlined in Scheme 9. Consecutive alkylations with bromoacetaldehyde dimethyl acetal and R^2-X gives **33**. Reaction of **33** with D-amino acid **5** using zinc in acetic acid provides lactam **34**. Bromoketone **36** is obtained from **34** by Wacker oxidation and bromonation. Treatment of bromoketone **36** with thiourea produces aminothiazole **37** (Markees, D. G.; Burger, A. *J. Am. Chem. Soc.* **1948**, *70*, 3329). Alkylation with R^4-X then provides **38**. Ester **38** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

Scheme 9



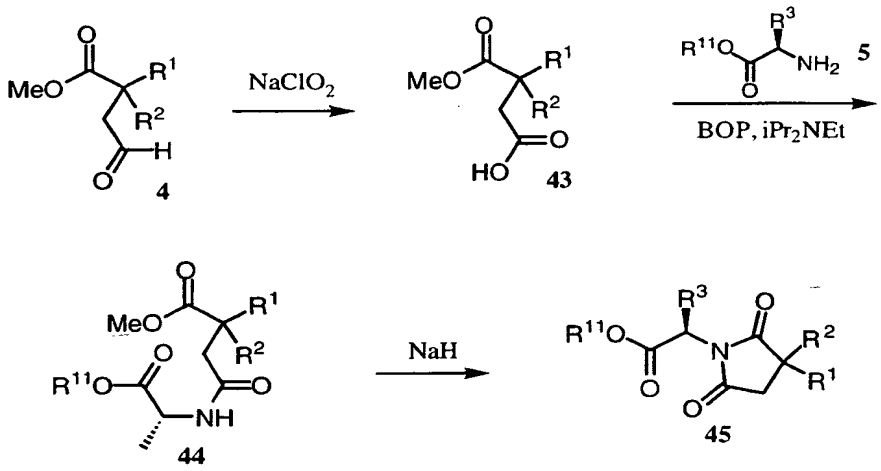
Another series of lactams of formula **42** with an imidazole substituent at the α position is prepared following the sequence outlined in Scheme 10. Consecutive alkylations with bromoacetaldehyde dimethyl acetal and R^2-X gives **41**. Reaction of **41** with D-amino acid **5** using zinc in acetic acid provides lactam **42**. Ester **42** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

Scheme 10



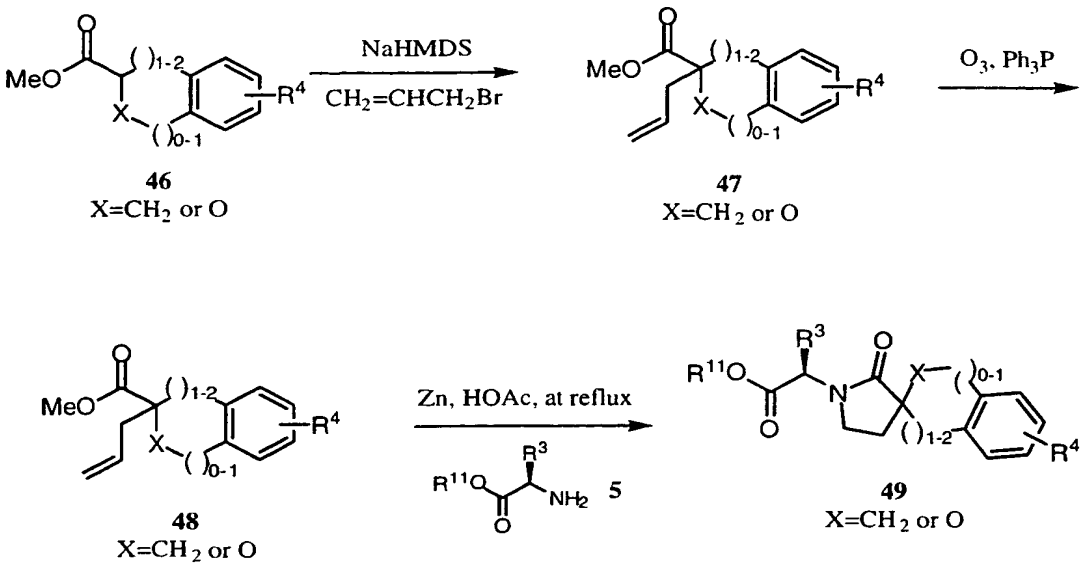
A series of succinimides of formula **45** is prepared from intermediate **4** (Scheme 11). The synthesis entails oxidation to carboxylic acid **43**, coupling with amino acid **5**, and succinimide formation. Ester **45** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

Scheme 11



A series of spirolactams of formula **49** is prepared from **46** (Scheme 12). The synthetic sequence is analogous to the strategy in Scheme 1. Ester **49** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

Scheme 12



46
X=CH_2 or O

47
X=CH_2 or O

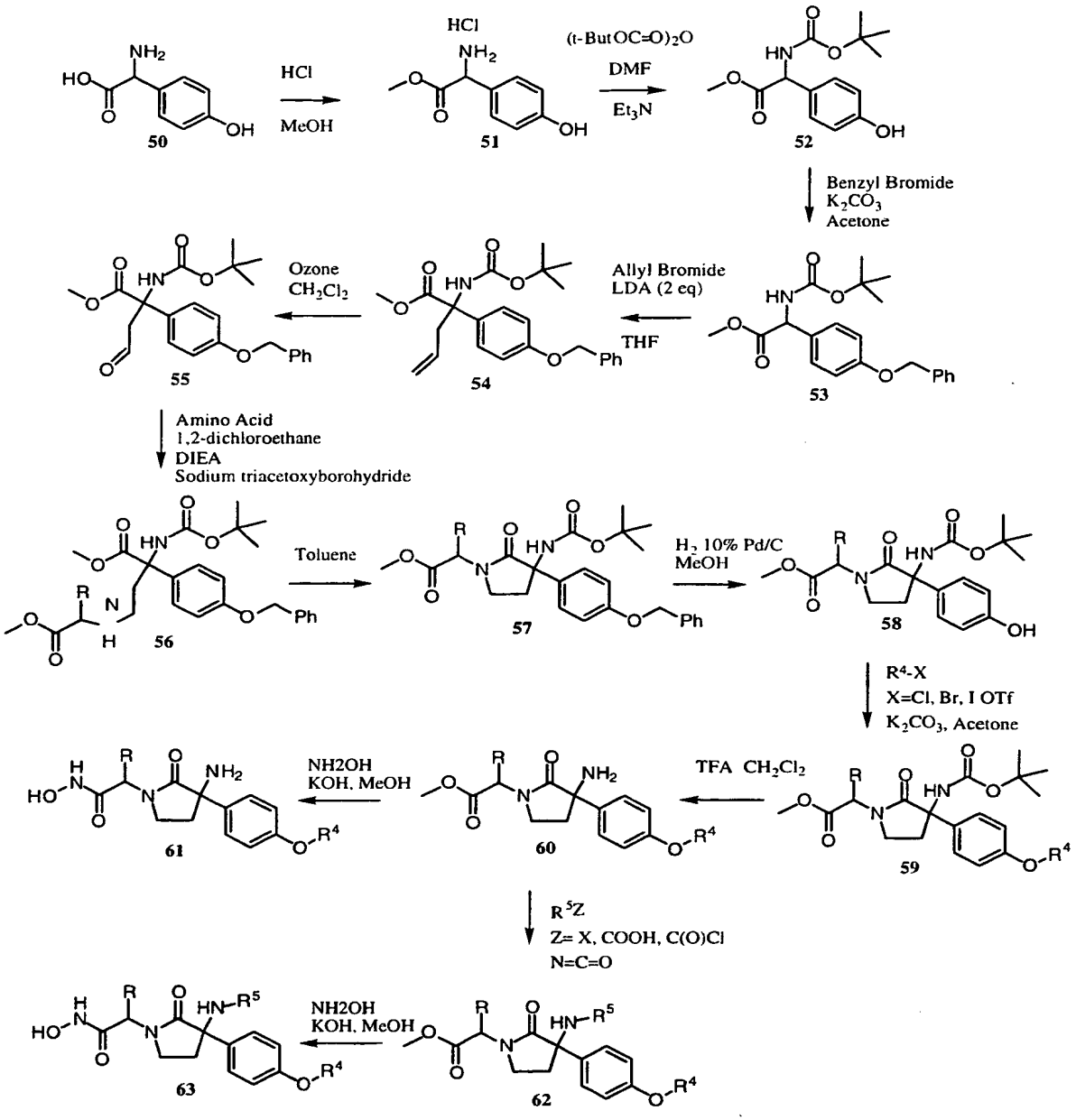
48
X=CH_2 or O

49
X=CH_2 or O

A variety of compounds of formula (I) wherein R^2 is NHR can be prepared by methods described in Scheme 13. The p-hydroxyglycine acid was converted to the methyl ester using methanol and HCl to give compound **51**, which was converted to the N-Boc protected amino acid **52** by methods described in the literature. The p-benzyloxyphenylglcine compound **53** was prepared by reacting the phenol compound **52** with benzyl bromide in acetone with a base such as potassium carbonate. The 2-allyl phenyl acetic acid compound **54**, was prepared by treating compound **53** with LDA (2 eq) and allyl bromide. The olefin compound **54** is oxidized to the aldehyde compound **55** using ozone and triphenylphosphine, then reacted with an appropriate amine to give the imine, which can be reduced with reagent similar to sodium triacetoxyborohydride, to give the amine compound **56**. The γ-lactam compound **57** is prepared by heating the amine compound **56** in an appropriate solvent such as toluene. The benzyl ether is removed by methods well known in the literature such as hydrogenation using palladium on carbon in hydrogen, to give compound **58**. The compound **59** is prepared by reacting the phenol **58** with an appropriately substituted halide or the like in acetone with a base such as potassium carbonate. The hydroxamic acid compound **61** was prepared from compound **59** by methods well known in the

literature for removing N-Boc groups and conversion of the methyl ester previously described. Alternatively the amine compound **60** can be treated with appropriately substituted acid chloride, isocyanate, carboxylic acid with coupling agents such as carbonyldiimidazole or the like, which are well known in the literature for making amide bonds. Alternatively the amine of compound **60** can be converted to an isocyanate by a variety of methods known in the literature like using phosgene and a base such as sodium carbonate, and reacting this with an appropriately substituted amine, to give compound **62**. The hydroxamic acid was prepared by methods previously described.

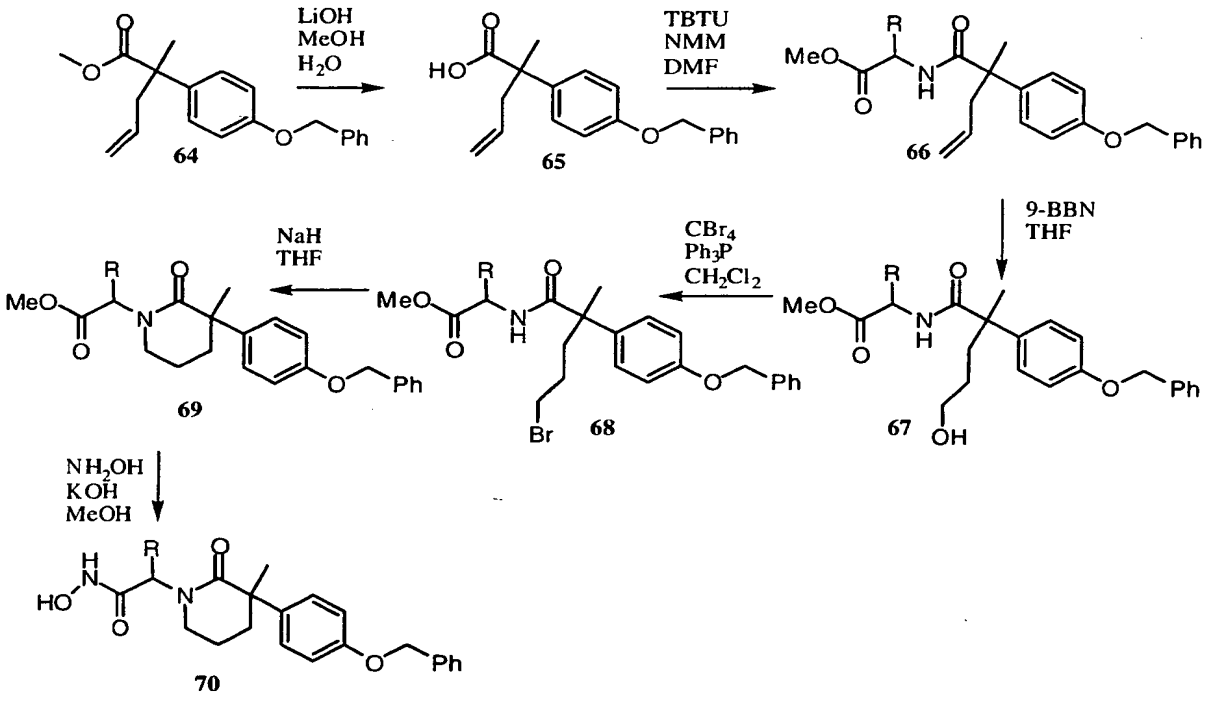
Scheme 13



A variety of compounds of formula (I) wherein the lactam is a six member ring can be prepared by methods described in Scheme 14. The ester compound **64** is converted to the acid compound **65** by methods well known in the literature, such as lithium hydroxide in methanol water, then coupled to an appropriately substituted amine by methods well described in the literature for making amide bonds, such as TBTU and N-methyl morpholine in DMF, to give compound **66**. The hydroxy

compound **67** was prepared from the olefin compound **66** by reduction with 9-BBN and oxidative workup with hydrogen peroxide. The δ-lactam **69** is prepared by converting the hydroxy of compound **67** to a leaving group by methods well known in the literature such as carbon tetrabromide and triphenylphosphine in methylene chloride. The bromide compound **68** was reacted with a base such as sodium hydride in THF to give the δ-lactam **69**. The hydroxamic acid compound **70** was prepared by methods previously described.

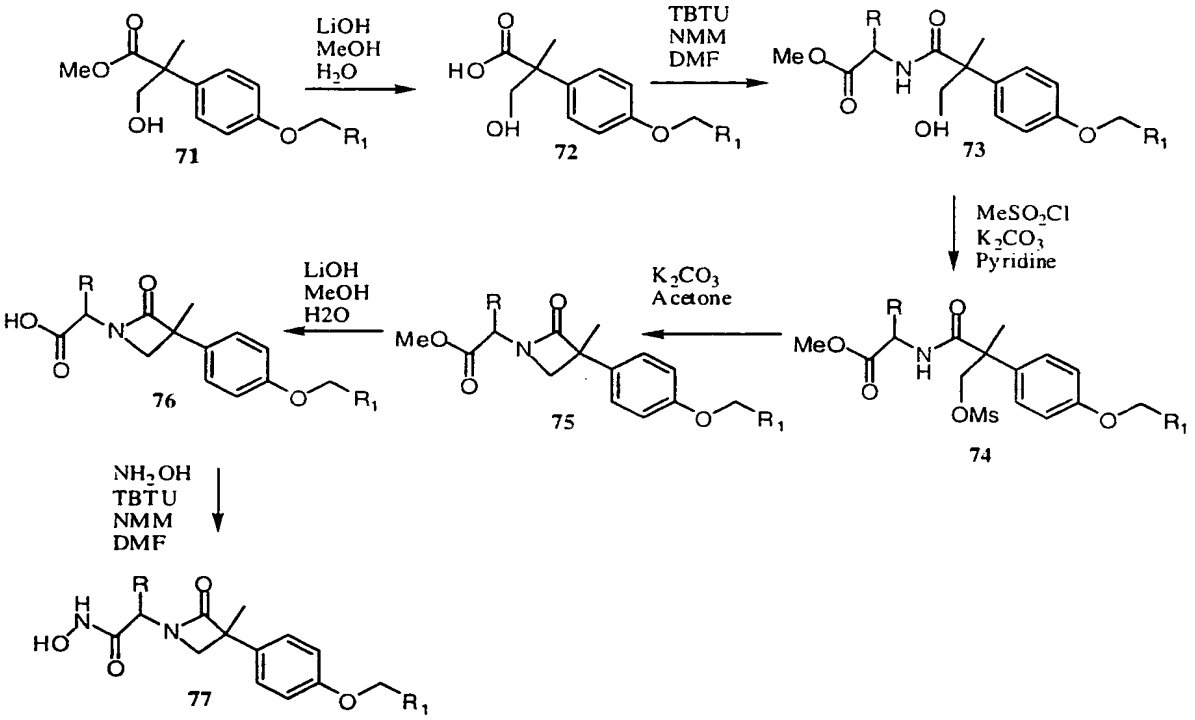
Scheme 14



A variety of compounds of formula (I) wherein the lactam is a four member ring can be prepared by methods described in Scheme 15. The ester compound **71** was converted to the acid compound **72** and coupled to an appropriately substituted amine by methods well known in the literature and previously described. The β-lactam **75** is prepared by converting the hydroxy of compound **73** to a leaving group by methods well known in the literature, such as methanesulfonyl chloride and potassium carbonate in pyridine. The methanesulfonate compound **74** was reacted with a base such as potassium

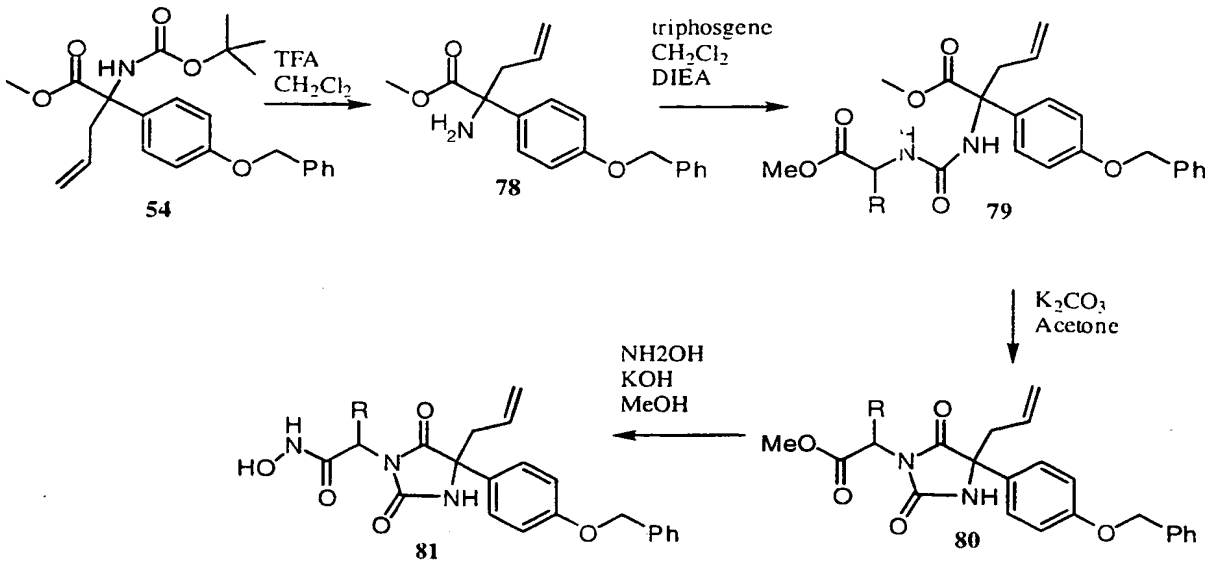
carbonate in acetone to give the β-lactam **75**. The hydroxamic acid compound **77** was prepared by methods previously described.

Scheme 15



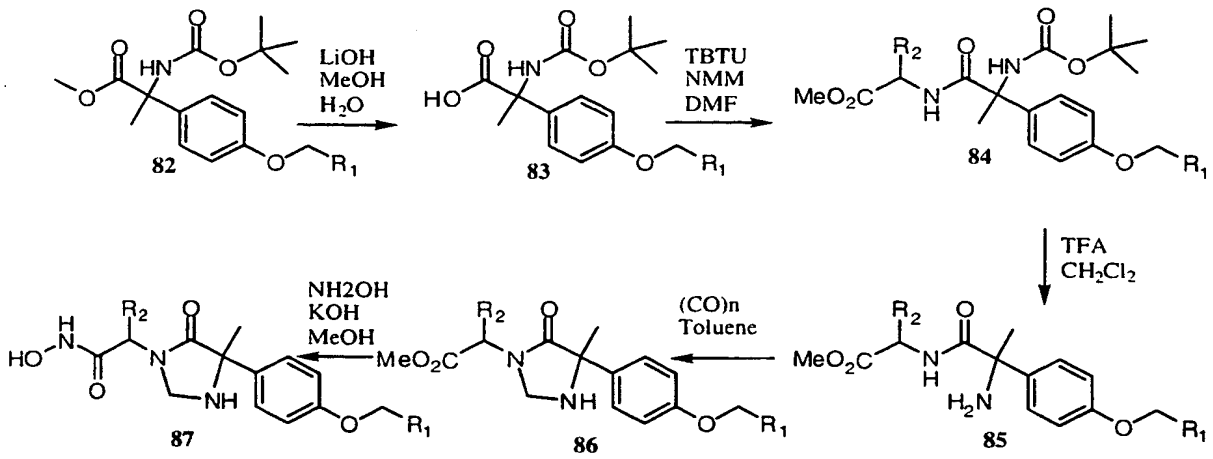
A variety of compounds of formula (I) wherein the lactam is replaced with a hydantoin ring can be prepared by methods described in Scheme 16. The amine compound **78** was prepared from the N-Boc compound **54** by methods previously described for the removal of Boc protecting groups. The urea compound **79** was prepared by converting the amine compound **78** to an isocyanate by methods well known in the literature and previously described, such as triphosgene and DIEA in methylene chloride and reacting this with an appropriately substituted amine. Alternatively, the amine **78** can be reacted with an isocyanate which is commercially available or can be prepared as described above. The hydantoin compound **80** was prepared by reacting the urea compound **79** with potassium carbonate in acetone. The final hydroxamic acid compound **81** was prepared by methods well documented previously.

Scheme 16



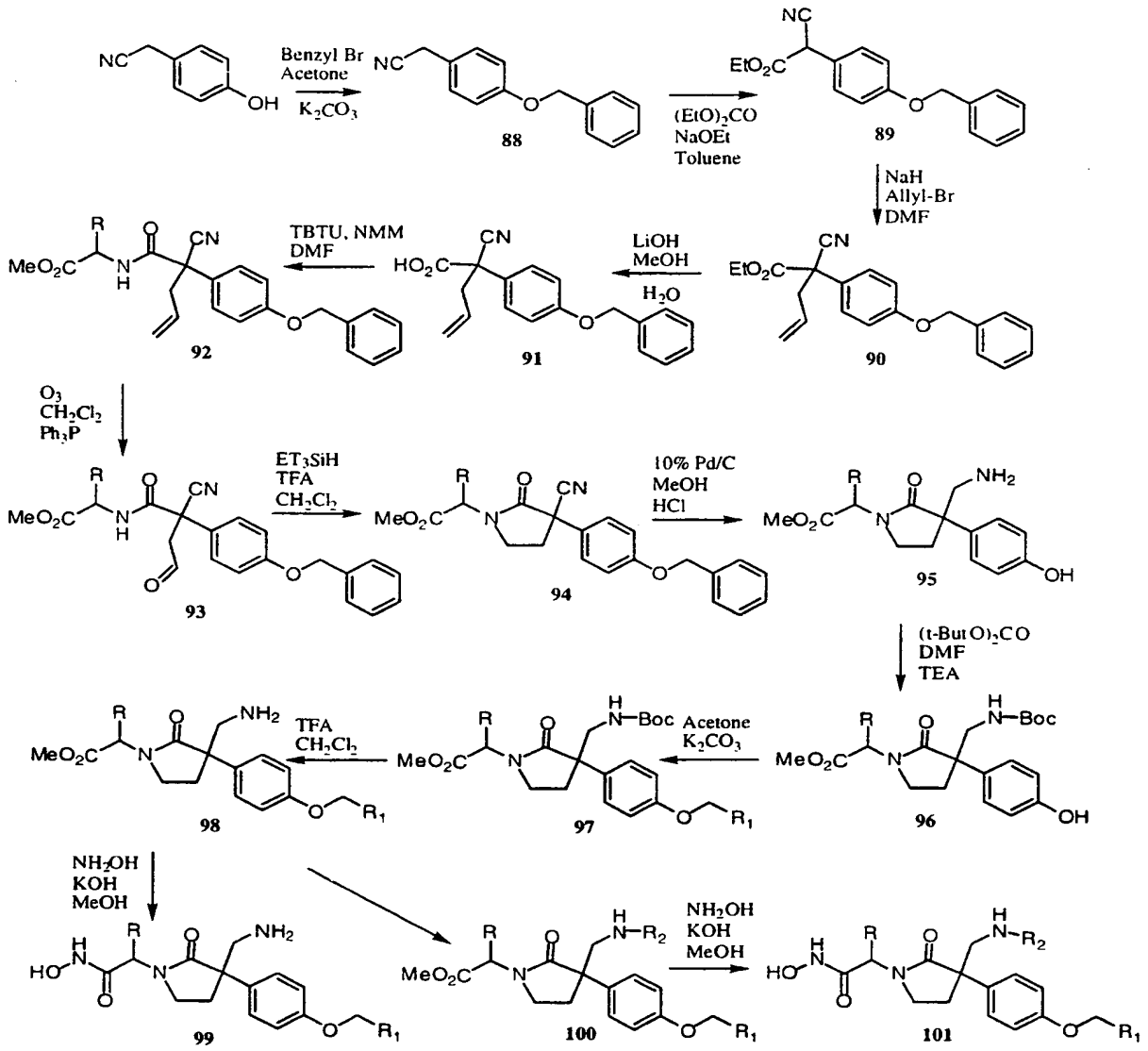
A variety of compounds of formula (I) wherein the lactam is replaced with a aminomethylene lactam ring can be prepared by methods described in Scheme 17. The diamino acid compound **84** was prepared from the 2-methyl phenylglycine compound **82**, by hydrolysis to the acid and coupling to an appropriately substituted amine a well described in the literature and previously detailed. The N-Boc group is remove by conventional methods previously described to give the amine compound **85**. The heterocyclic compound **86** was prepared by reacting the amine compound **85** with paraformaldehyde in toluene at elevated temperatures. The final hydroxamic acid compound **87** was prepared by methods well documented previously.

Scheme 17



A variety of compounds of formula (I) wherein R^2 is CH_2NHR can be prepared by methods described in Scheme 18. The cyanoacetate compound **89** was prepared by reacting the p-hydroxyphenylacetonitrile with benzyl bromide in acetone with potassium carbonate to give compound **88**, which was in turn reacted with sodium ethoxide and diethylcarbonate in toluene at elevated temperatures. The allyl cyanoacetate compound **90** was prepared from the cyanoacetate compound **89** by generating the anion with a base such as sodium hydride and reacting this with allyl bromide in DMF. The nitrile lactam compound **94** was prepared by a sequence of steps previously described in several other Schemes. The N-Boc methyleneamine compound **96** was prepared by reduction of the nitrile lactam compound **94**, using palladium on carbon with HCl in methanol, to give the amino compound **95** which was then protected by conventional methods with a Boc group to give compound **96**. The final hydroxamic acid compounds **99** and **101** were prepared by methods previously described.

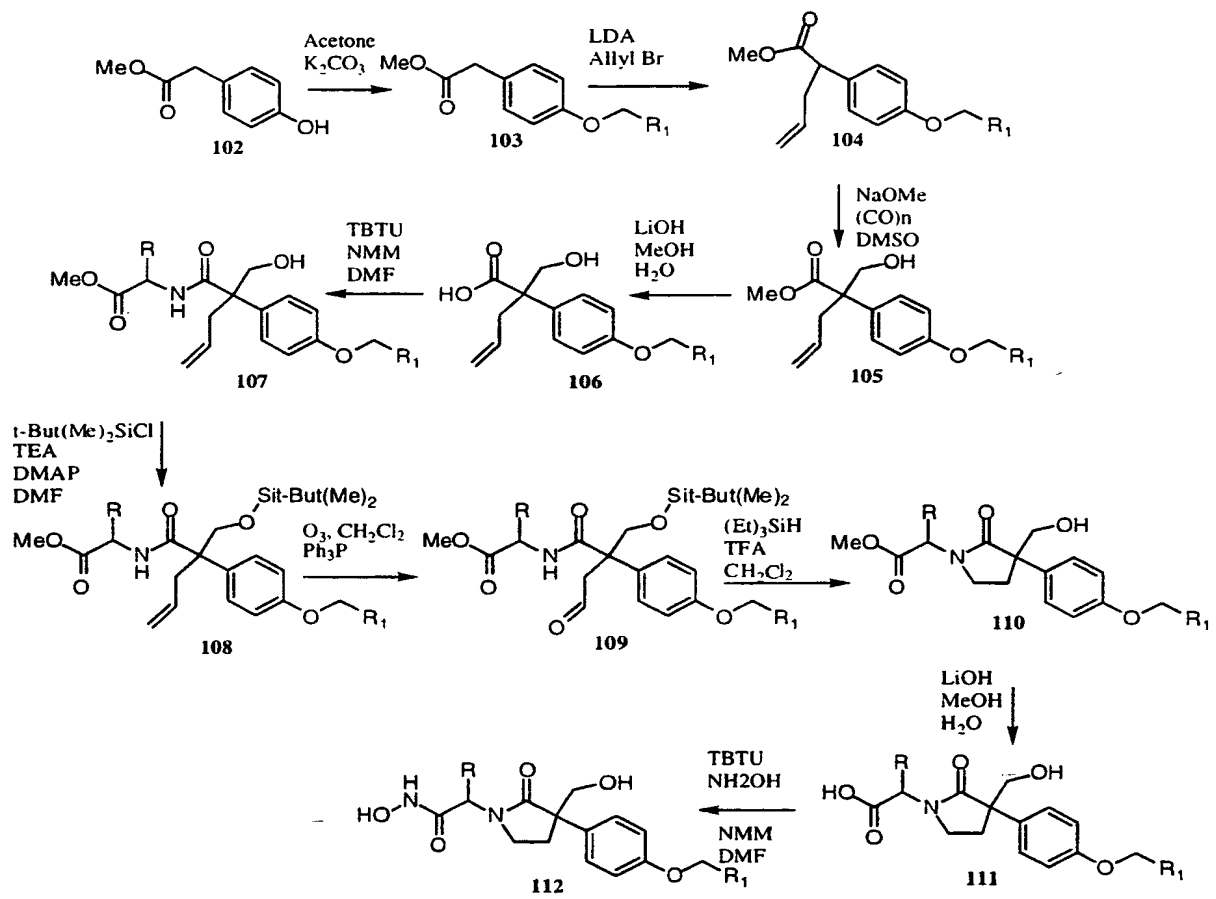
Scheme 18



A variety of compounds of formula (I) wherein R^2 is CH_2OH can be prepared by methods described in Scheme 19. The allyl compound **104** was prepared from p-hydroxyphenyl acetate, by reaction with benzyl bromide and potassium carbonate in acetone as previously described and then treating the benzyloxy phenyl acetate compound **103** with LDA and allyl bromide in THF. The methylene hydroxy compound **105** was prepared by treating the benzyloxy phenyl acetate compound **103** with paraformaldehyde and sodium methoxide in DMSO. The hydrolysis of the ester and coupling of the carboxylic acid to

an appropriately substituted amine was described earlier to give the compound **107**. The protected O-silyl compound **108** was prepared by methods well described in the literature, then oxidation to the aldehyde compound **109** with ozone was described previously. The lactam compound **110** was prepared from the aldehyde compound **109** by treatment with triethyl silane and TFA in methylene chloride at ambient temperatures. The final hydroxamic acid compound **112** was prepared by methods previously described.

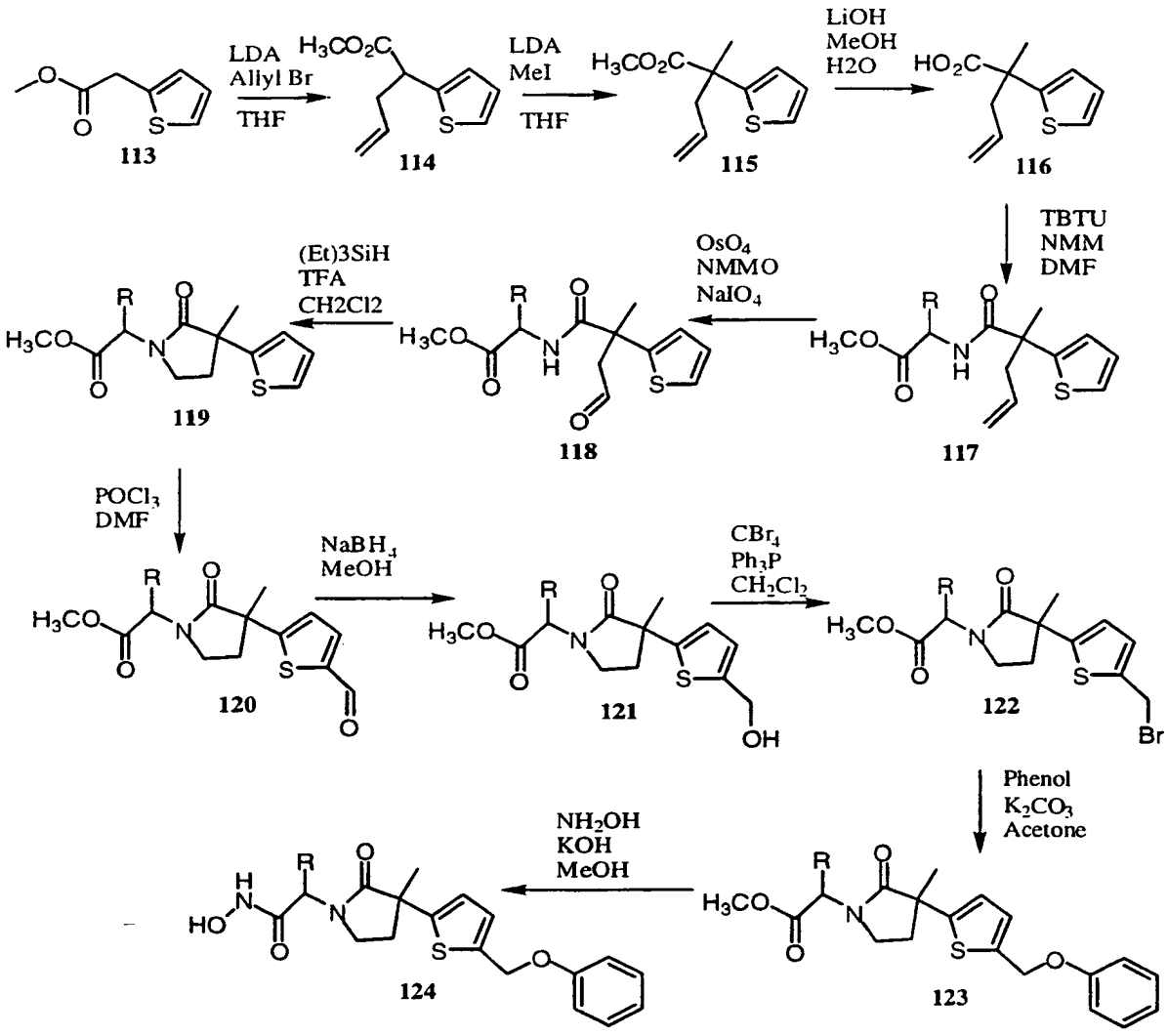
Scheme 19



A variety of compounds of formula (I) wherein R^1 is a heterocycle, such as thiophene, can be prepared by methods described in Scheme 20. The thiophene substituted compound **115** was prepared by treating the thiophene acetate compound **113** with LDA and allyl bromide to give compound **114**, and subsequently with LDA and methyl iodide in THF. The thiophene

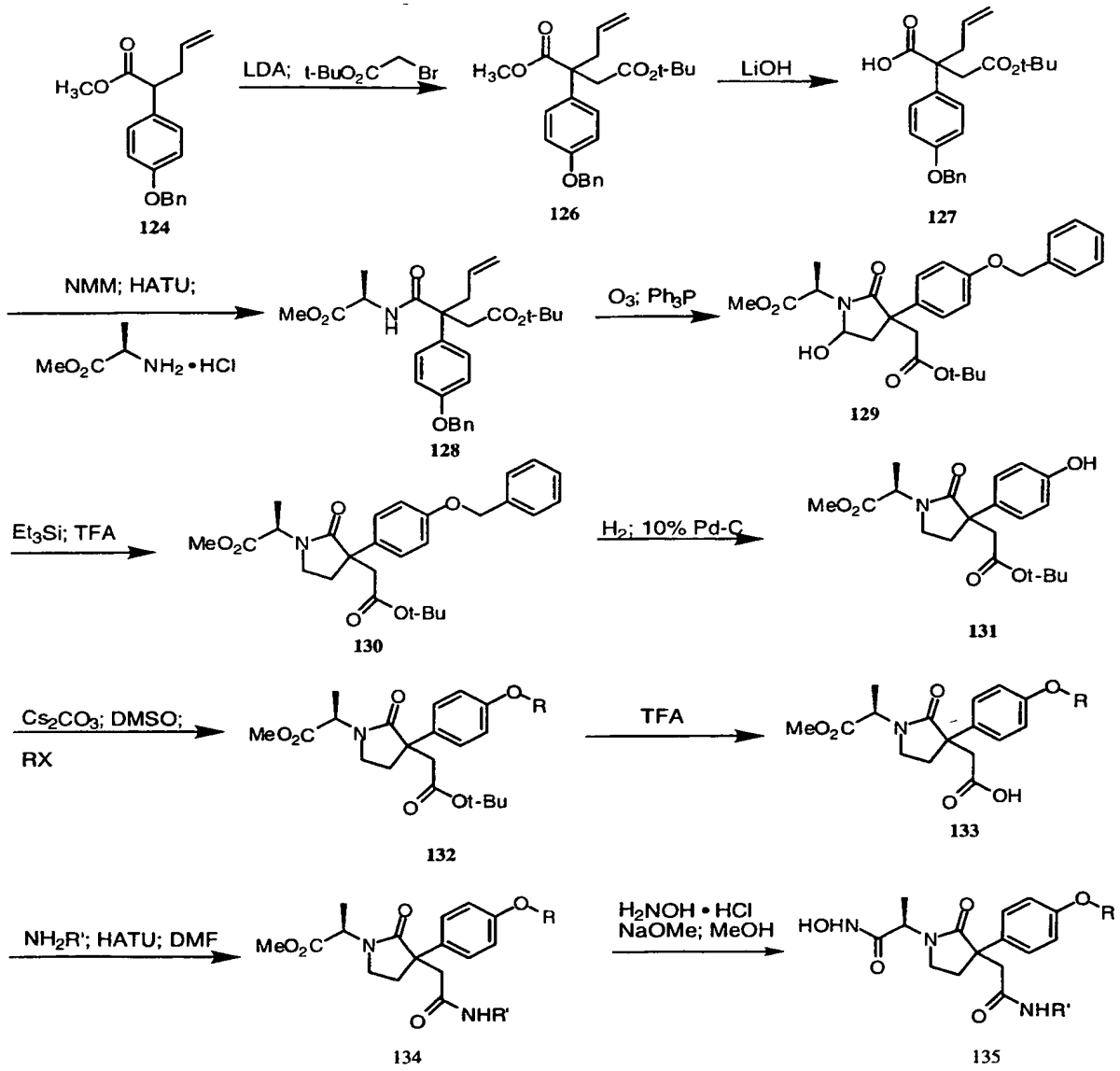
compound **117** was prepared by methods previously detailed for ester hydrolysis to the acid and coupling the carboxylic acid to an amine. The oxidation of the olefin compound **117**, to the aldehyde compound **118**, was performed by the action of osmium tetraoxide and NMMO, to give the diol, then treatment with NaIO4. The formation of the lactam ring compound **119** was previously described using triethylsilane and TFA in methylene chloride. The aldehyde thiophene compound **120** was prepared by chemistry well described in the literature, using phosphorus oxychloride in DMF. The aldehyde compound **120** was reacted with sodium borohydride in methanol to give alcohol compound **121** which was reacted with carbon tetrabromide and triphenyl phosphine to give the bromide compound **122**. The bromide was treated with phenol and potassium carbonate in acetone to give the phenyl ether compound **123**. The final hydroxamic acid compound **124** was prepared by methods previously described.

Scheme 20



Another series of lactams of formula **135** is prepared following the sequence outlined in Scheme 21. Ester **124** is alkylated with t-butyl bromoacetate to give **126**. Ester **126** is converted to **132** following previously described sequence. Removal of t-butyl group and coupling with NH_2R' under literature well known conditions gives **134**. Ester **134** is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

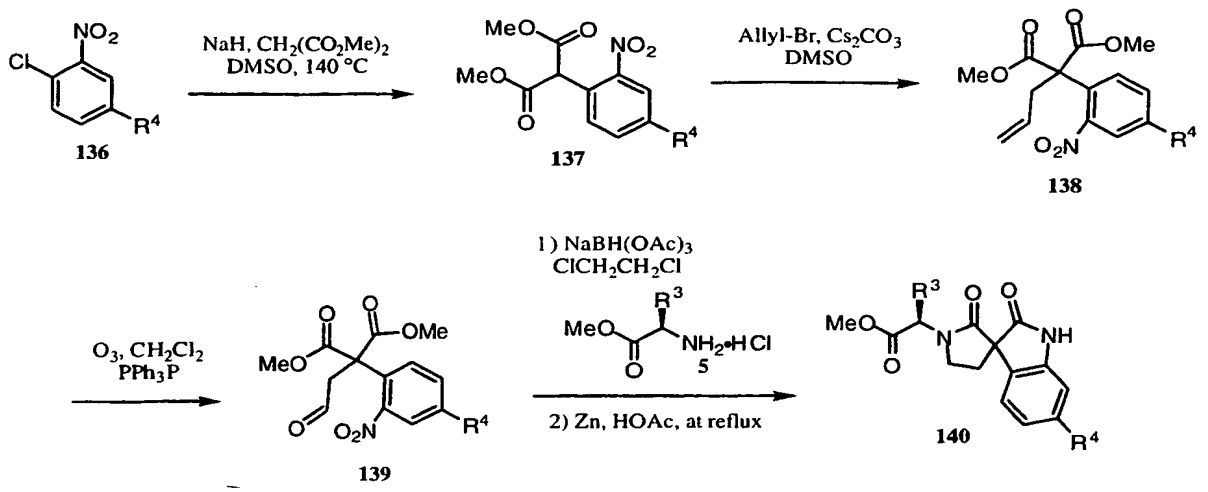
Scheme 21



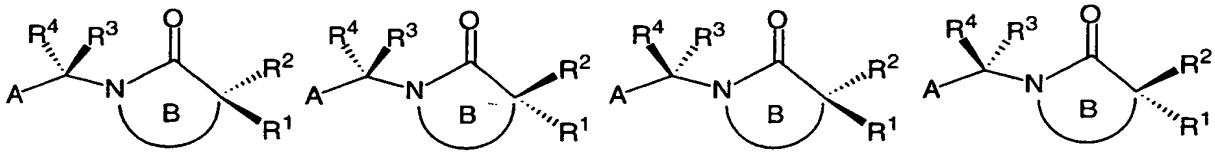
Another series of spirolactams of formula **140** is prepared following the sequence outlined in Scheme 22. Reaction of **136** with dimethyl malonate via S_{NAr} replacement gives diester **137**. Aldehyde **139** is prepared from **137** by allylation and ozonolysis. Reaction of aldehyde **139** with **5** gives secondary amine under reductive amination conditions. Treatment with zinc in acetic acid under reflux affects nitro reduction and spirocyclization in one pot to give **140**. Ester

140 is converted to the hydroxamic acid following the sequences outlined in Scheme 2.

Scheme 22



One diasteriomer of a compound of Formula I may display superior activity compared with the others. Thus, the following stereochemistries are considered to be a part of the present invention.



Ia Ib Ic Id

When required, separation of the racemic material can be achieved by HPLC using a chiral column or by a resolution using a resolving agent such as camphonic chloride as in Steven D. Young, et al, *Antimicrobial Agents and Chemotheraphy* **1995**, 2602-2605. A chiral compound of Formula I may also be directly synthesized using a chiral catalyst or a chiral ligand, e.g., Andrew S. Thompson, et al, *Tet. lett.* **1995**, *36*, 8937-8940).

Other features of the invention will become apparent in the course of the following descriptions of exemplary

embodiments which are given for illustration of the invention and are not intended to be limiting thereof.

Examples

Abbreviations used in the Examples are defined as follows: "1 x" for once, "2 x" for twice, "3 x" for thrice, "°C" for degrees Celsius, "eq" for equivalent or equivalents, "g" for gram or grams, "mg" for milligram or milligrams, "mL" for milliliter or milliliters, "^{1}H" for proton, "h" for hour or hours, "M" for molar, "min" for minute or minutes, "MHz" for megahertz, "MS" for mass spectroscopy, "NMR" for nuclear magnetic resonance spectroscopy, "rt" for room temperature, "tlc" for thin layer chromatography, "v/v" for volume to volume ratio. "α", "β", "R" and "S" are stereochemical designations familiar to those skilled in the art.

Example 1

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-(phenylmethoxy)phenyl]-1-pyrrolidineacetamide

(1a) A 1.0 M tetrahydrofuran solution of sodium bis(trimethylsilyl)amide (254 mL, 1.3 eq) was added over 1 h to methyl 4-benzyloxyphenylacetate (50.00 g, 195 mmol) in tetrahydrofuran (600 mL) at -78 °C. After 1 h at -78 °C, iodomethane (18.2 mL, 1.5 eq) was added. After 2 h at -20 °C, saturated ammonium chloride (400 mL), water (600 mL), ether (500 mL) and hexane (500 mL) were added. The two phases were separated and the aqueous phase extracted with 1:1 (v/v) ether-hexane (2 x 650 mL). The combined organic extracts were washed successively with water (2 x 500 mL), brine (400 mL) and dried (MgSO4). Removal of solvent *in vacuo* provided the desired product (49.58 g, 94%) as a yellow viscous oil. MS found: $(M+NH_4)^+$ = 288.

(1b) Following a procedure analogous to (1a), the material from (1a) (48.66 g, 180 mmol) was treated with 1.0 M tetrahydrofuran solution of sodium bis(trimethylsilyl)amide (234 mL, 1.3 eq) at -78 °C and alkylated with allyl bromide (23.4 mL, 1.5 eq) at -20 °C. Workup and concentration gave

the desired product (54.77 g, 98%) as a pale yellow solid. MS found: $(M+H)^+$ = 311, $(M+NH_4)^+$ = 328.

(1c) Ozone was bubbled through a solution of the olefin from (1b) (54.0 g, 174 mmol) in dichloromethane (500 mL) at -78 °C until starting material disappeared by TLC. The mixture was purged with nitrogen and treated with triphenylphosphine (54.77 g, 1.2 eq). After 1 h at ambient temperature, the mixture was concentrated *in vacuo*. The residue was purified by short silica gel column (ethyl acetate-hexane, 20:80) to give the desired aldehyde (44.65 g, 82%) as a white solid. MS found: $(M+H)^+$ = 313, $(M+NH_4)^+$ = 330.

(1d) Zinc powder (93.74 g, 10 eq) was added in several portions to the aldehyde from (1c) (44.73 g, 143 mmol) and D-alanine methyl ester hydrochloride (22.00 g, 1.1 eq) in acetic acid (1 L) at 5-10 °C. The mixture was heated to reflux for 4 h and then cooled to rt. Following addition of chloroform (1 L), the mixture was filtered and the solid residue washed with 1:1 ethanol-chloroform (500 mL). Following removal of solvent *in vacuo*, ethyl acetate (1 L) was added and the precipitate was removed by filtration. The filtrate was concentrated and purified by silica gel chromatography (ethyl acetate-hexane, 35:65 then 40:60 then 60:40) to give a 1:1 mixture of lactams (42.30 g, 81%). The mixture was separated by repeated silica gel chromatography (ethyl acetate-hexane, 40:60). MS found: $(M+H)^+$ = 368.

(1e) Preparation of hydroxylamine/potassium hydroxide solution: A solution of potassium hydroxide (2.81 g, 1.5 eq) in methanol (7 mL) was added to a hot solution of hydroxylamine hydrochloride (2.34 g, 33.7 mmol) in methanol (12 mL). After the mixture was cooled to room temperature, the precipitate was removed by filtration. The filtrate was used fresh and assumed hydroxylamine concentration of 1.76 M.

The freshly prepared 1.76 M solution of hydroxylamine (2.3 mL, 4 eq) was added to the less polar isomer from (1d) (369.2 mg, 1.00 mmol) in methanol (2 mL) at rt. After 1 h at this temperature, same portion of hydroxylamine was added and the mixture was stirred for additional 30 min. Upon acidification to pH 4-5 with 1 N HCl, the desired hydroxamic

acid precipitated out. The product was collected by filtration and washed with water (3 x) to give a white solid (322.6 mg, 87%). MS found: $(M-H)^-$ = 367.

(1f) Following a procedure analogous to (1e), the more polar isomer from (1d) (378.6 mg, 1.03 mmol) was reacted with hydroxylamine. After adjusting to pH 4 with 1 N HCl, methanol was removed *in vacuo*. The aqueous residue was extracted with ethyl acetate, dried ($MgSO_4$) and concentrated. Silica gel chromatography (methanol-dichloromethane, 5:95 then 10:90) provided the desired hydroxamic acid (84.0 mg, 22%) as a white solid. MS found: $(M-H)^-$ = 367.

Example 2

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-(4-methoxyphenyl)-1-pyrrolidineacetamide

(2a) A 1.0 M tetrahydrofuran solution of sodium bis(trimethylsilyl)amide (139 mL, 1.1 eq) and methyl 4-methoxyphenylacetate (20.0 mL, 126 mmol) were added successively to tetrahydrofuran (500 mL) at -78 °C. After 1 h at -78 °C, allyl bromide (16.4 mL, 1.5 eq) was added. After 1.5 h at -78 °C, the cold bath was removed and the mixture stirred at ambient temperature for 1 h. Following addition of saturated ammonium chloride (200 mL), water (800 mL), and hexane (1000 mL), the two phases were separated and the aqueous phase extracted with hexane (2 x 500 mL). The combined organic extracts were washed successively with water (2 x 100 mL), brine (100 mL), dried ($MgSO_4$) and concentrated to provide the product (28.00 g) as a yellow liquid. This material was used in the subsequent reaction without purification.

(2b) Following a procedure analogous to (1a), the crude material from (2a) (8.20 g) was reacted with potassium bis(trimethylsilyl)amide and iodomethane to yield the desired product (8.50 g, 97%) as a yellow oil. MS found: $(M+H)^+$ = 235, $(M+NH_4)^+$ = 252.

(2c) Ozone was bubbled through a solution of the olefin from (2b) (8.40 g, 35.85 mmol) in dichloromethane (500 mL) at -78

°C until the solution turned blue. The mixture was purged with nitrogen, treated with dimethyl sulfide (13.1 mL, 5 eq) and stirred at rt overnight. Concentration in vacuo provided crude aldehyde (10.65 g). The material was used in the subsequent reaction without purification.

(2d) Following a procedure analogous to (1d), the aldehyde from (2c) (6.36 g) was reacted with D-alanine methyl ester hydrochloride. Silica gel chromatography (ethyl acetate-hexane, 35:65 then 40:60) gave less polar lactam (630 mg), more polar lactam (1.12 g), and a 5:3 mixture of the two isomers (1.17 g). The total yield of the two isomers is 2.92 g (47% for two steps). MS found: $(M+H)^+$ = 292.

(2e) Following a procedure analogous to (1e), the less polar isomer from (2d) (226.8 mg, 0.778 mmol) was reacted with hydroxylamine. Preparative thin layer chromatography (methanol-dichloromethane, 10:90) gave the hydroxamic acid (183.3 mg, 81%) as a light yellow powder. MS found: $(M-H)^-$ = 291.

(2f) Following a procedure analogous to (1e), the more polar isomer from (2d) (197.0 mg, 0.676 mmol) was reacted with hydroxylamine. Preparative thin layer chromatography (methanol-dichloromethane, 10:90) gave the hydroxamic acid (158.4 mg, 80%) as a light yellow powder. MS found: $(M-H)^-$ = 291.

Example 3

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-[4-(1-methylethoxy)phenyl]-2-oxo-1-pyrrolidineacetamide

(3a) A 1:1 mixture of the benzyl ether from (1d) (16.26 g, 44.25 mmol), 20% palladium hydroxide on carbon (3.0 g) and methanol (500 mL) was stirred under balloon pressure hydrogen for 2 h. The catalyst was removed by filtration. The filtrate was concentrated to give the phenol (11.87 g, 97%) as a 1:1 mixture of two isomers. MS found: $(M+H)^+$ = 278.

(3b) A mixture of the phenol from (3a) (460 mg, 1.66 mmol) and N,N'-dimethyl-O-isopropylisourea (5 mL) was heated to 70 °C for 4 h and then cooled to rt. Following addition of acetic acid (2 mL) and dichloromethane (2 mL), the mixture was

stirred for 30 min. The mixture was then filtered through a silica gel pad and the filter cake washed with ethyl acetate-hexane (40:60). The filtrate was concentrated and purified by silica gel chromatography (ethyl acetate-hexane, 40:60) to give the isopropyl ether (123.2 mg, 23%) as a 1:1 mixture of two isomers. MS found: $(M+H)^+ = 320$.

(3c) Following a procedure analogous to (1e), the isopropyl ether from (3b) (99.1 mg, 0.310 mmol) was reacted with hydroxylamine to give the hydroxamic acid (29.1 mg, 29%) as a 1:1 mixture of two isomers. MS found: $(M-H)^- = 319$.

Example 4

[1(*R*)]-3-[4-(1,1-dimethylethoxy)phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide

(4a) Following a procedure analogous to (3b), the phenol from (3a) (270 mg, 0.97 mmol) was reacted with N,N'-dimethyl-O-t-butylisourea. Silica gel chromatography (ethyl acetate-hexane, 20:80) gave the t-butyl ether (50.2 mg, 15%) as a 1:1 mixture of two isomers. MS found: $(M+H)^+ = 334$.

(4b) Following a procedure analogous to (1e), the t-butyl ether from (4a) (45 mg, 0.135 mmol) was reacted with hydroxylamine to give the hydroxamic acid (26.1 mg, 58%) as a 1:1 mixture of two isomers. MS found: $(M-H)^- = 333$.

Example 5

[1(*R*)]-3-(4-(cyclohexyloxy)phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide

(5a) Following a procedure analogous to (3b), the phenol from (3a) (350 mg, 1.26 mmol) was reacted with N,N'-dimethyl-O-cyclohexylisourea. Silica gel chromatography (ethyl acetate-hexane, 40:60) gave the cyclohexyl ether (70 mg, 15%) as a 1:1 mixture of two isomers. MS found: $(M+H)^+ = 360$.

(5b) Following a procedure analogous to (1e), the cyclohexyl ether from (5a) (61.5 mg, 0.171 mmol) was reacted with hydroxylamine to give the hydroxamic acid (39.5 mg, 64%) as a 1:1 mixture of two isomers. MS found: $(M-H)^- = 359$.

Example 6

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-[4-(1,1-dimethylethyl)phenylmethoxy]phenyl]-1-pyrrolidineacetamide

(6a) Following a procedure analogous to (3a), the more polar isomer from (1d) (2.35 g, 6.40 mmol) was hydrogenolyzed to give the phenol (1.77 g, 100%) as a colorless viscous oil. MS found: $(M+H)^+ = 278$.

(6b) Cesium carbonate (225 mg, 1.8 eq) was added to a solution of the phenol from (6a) (106.3 mg, 0.383 mmol), and p-t-butylbenzyl bromide (174 mg, 2 eq) in methyl sulfoxide (2 mL). After 1.5 h at rt, saturated ammonium chloride (3 mL) and ethyl acetate (100 mL) were added. The mixture was washed with water (2x5 mL), brine (5 mL), dried (MgSO4) and concentrated. Silica gel chromatography (ethyl acetate-hexane, 30:70 then 35:75) gave the ether (149.5 mg, 92%) as a colorless oil. MS found: $(M+H)^+ = 424$.

(6c) Following a procedure analogous to (1f), the ester from (6b) (142.0 mg, 0.335 mmol) was reacted with hydroxylamine. Upon neutralization and removal of methanol *in vacuo*, product precipitated out of solution. The precipitate was collected by filtration and washed with water several times to give the hydroxamic acid (113.3 mg, 80%) as a white powder. MS found: $(M-H)^- = 423$.

Example 7

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-(trans-3-phenyl-2-propenyloxy)phenyl]-1-pyrrolidineacetamide

(7a) Following a procedure analogous to (6b), the phenol from (3a) (510 mg, 1.84 mmol) was reacted with cinnamyl bromide and potassium carbonate in N,N-dimethylformamide. Silica gel chromatography (ethyl acetate-hexane, 30:70 then 40:60) gave less polar isomer (87 mg), more polar isomer (102 mg), and a 1:1 mixture of the two isomers (300 mg). The total yield is 489 mg (68%). MS found: $(M+H)^+ = 394$.

(7b) Following a procedure analogous to (1e), the less polar isomer from (7a) (82 mg, 0.208 mmol) was reacted with hydroxylamine. Silica gel chromatography (methanol-

dichloromethane, 5:95) gave the hydroxamic acid (37 mg, 45%) as a solid. MS found: $(M-H)^-$ = 393.

(7c) Following a procedure analogous to (1e), the more polar isomer from (7a) (97 mg, 0.247 mmol) was reacted with hydroxylamine. Silica gel chromatography (methanol-dichloromethane, 5:95) gave the hydroxamic acid (52 mg, 54%) as a solid. MS found: $(M-H)^-$ = 393.

Example 8

[1(*R*)]-3-[4-[(3-methylphenyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide

(8a) Following a procedure analogous to (6b), the phenol from (3a) (277.6 mg, 1.00 mmol) was reacted with α-bromo-m-xylene and cesium carbonate in N,N-dimethylformamide. Silica gel chromatography (ethyl acetate-hexane, 30:70 then 40:60) gave the less polar isomer (53 mg), the more polar isomer (50.8 mg), and a 1:1 mixture the two isomers (40.0 mg). The total yield is 143.8 mg (38%). MS found: $(M+H)^+$ = 382.

(8b) Following a procedure analogous to (1e), the less polar isomer from (8a) (53 mg, 0.139 mmol) was reacted with hydroxylamine. Silica gel chromatography (methanol-dichloromethane, 5:95) gave the hydroxamic acid (31.7 mg, 60%) as a solid. MS found: $(M-H)^-$ = 381.

(8c) Following a procedure analogous to (1e), the more polar isomer from (8a) (50.8 mg, 0.133 mmol) was reacted with hydroxylamine. Silica gel chromatography (methanol-dichloromethane, 5:95) gave the hydroxamic acid (33.7 mg, 66%) as a solid. MS found: $(M-H)^-$ = 381.

Example 9

[1(*R*)]-3-[4-[(3,5-dimethylphenyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide

(9a) Following a procedure analogous to (6b), the phenol from (3a) (450 mg, 1.62 mmol) was reacted with α-bromomesitylene and cesium carbonate in N,N-dimethylformamide. Silica gel chromatography (ethyl acetate-hexane, 30:70 then 40:60) gave the less polar isomer (130.8 mg), the more polar isomer (125.0

mg), and a 1:1 mixture of the two isomers (73.7 mg). The total yield is 329.5 mg (51%). MS found: $(M+H)^+$ = 396.

(9b) Following a procedure analogous to (1e), the less polar isomer from (9a) (50 mg, 0.126 mmol) was reacted with hydroxylamine. Silica gel chromatography (methanol-dichloromethane, 5:95) gave the hydroxamic acid (37.6 mg, 75%) as a solid. MS found: $(M-H)^-$ = 395.

(9c) Following a procedure analogous to (1e), the more polar isomer from (9a) (46.0 mg, 0.116 mmol) was reacted with hydroxylamine. Silica gel chromatography (methanol-dichloromethane, 5:95) gave the hydroxamic acid (25.0 mg, 54%) as a solid. MS found: $(M-H)^-$ = 395.

Example 10

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-2-oxo-3-[4-(2-propenyloxy)phenyl]-1-pyrrolidineacetamide

(10a) Following a procedure analogous to (6b), the phenol from (3a) (480 mg, 1.73 mmol) was reacted with allyl bromide and potassium carbonate in N,N-dimethylformamide. Silica gel chromatography (ethyl acetate-hexane, 30:70 then 40:60) gave the less polar isomer (111 mg), the more polar isomer (57 mg), and a 5:6 mixture of the two isomers (45.6 mg). The total yield is 213.6 mg (39%). MS found: $(M+H)^+$ = 318.

(10b) Following a procedure analogous to (1e), the less polar isomer from (10a) (110 mg, 0.347 mmol) was reacted with hydroxylamine. Silica gel chromatography (methanol-dichloromethane, 5:95) gave the hydroxamic acid (68 mg, 62%) as a solid. MS found: $(M-H)^-$ = 317.

(10c) Following a procedure analogous to (1e), the more polar isomer from (10a) (57 mg, 0.18 mmol) was reacted with hydroxylamine. Silica gel chromatography (methanol-dichloromethane, 5:95) gave the hydroxamic acid (51 mg, 89%) as a solid. MS found: $(M-H)^-$ = 317.

Example 11

[1(*R*)]-3-[4-[(3-cyanophenyl)methoxy]phenyl]-*N*-hydroxy-α,3-dimethyl-2-oxo-1-pyrrolidineacetamide

(11a) Following a procedure analogous to (6b), the phenol from (6a) (99.7 mg, 0.360 mmol) was reacted with α-bromo-m-tolunitrile. Silica gel chromatography (ethyl acetate-hexane, 40:60 then 50:50) gave the ether (130.2 mg, 92%) as a colorless glass. MS found: $(M+H)^+$ = 393.

(11b) Following a procedure analogous to (1e), the ester from (11a) (56.9 mg, 0.145 mmol) was reacted with hydroxylamine. Silica gel chromatography (methanol-dichloromethane, 8:92 then 15:85) gave the hydroxamic acid (24 mg, 42%) as a viscous oil. MS found: $(M-H)^-$ = 392.

Example 12

[1(*R*)]-*N*-hydroxy-α-3-dimethyl-3-[4-[(2-nitrophenyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide

(12a) Following a procedure analogous to (5b), the phenol from (5a) (93.0 mg, 0.335 mmol) was reacted with o-nitrobenzyl bromide. Silica gel chromatography (ethyl acetate-hexane, 40:60) gave product (130 mg, 94%) as a colorless glass. MS found: $(M+H)^+$ = 413.

(12b) Following a procedure analogous to (1e), the ester from (12a) (110 mg, 0.267 mmol) was reacted with hydroxylamine to give the hydroxamic acid (106.6 mg, 97%) as a solid. MS found: $(M-H)^-$ = 412.

Example 13

[1(*R*)]-*N*-hydroxy-α-3-dimethyl-3-[4-[(3-nitrophenyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide

(13a) Following a procedure analogous to (6b), the phenol from (6a) (95.2 mg, 0.343 mmol) was reacted with m-nitrobenzyl bromide. Silica gel chromatography (ethyl acetate-hexane, 40:60) gave the desired product (57.6 mg, 41%). MS found: $(M+H)^+$ = 413.

(13b) Following a procedure analogous to (1e), the ester from (13a) (50 mg, 0.121 mmol) was reacted with hydroxylamine to give the hydroxamic acid (44.3 mg, 89%) as a solid. MS found: $(M-H)^-$ = 412.

Example 14

[1(*R*)]-*N*-hydroxy-α,3-dimethyl-3-[4-[(4-nitrophenyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide

(14a) Following a procedure analogous to (6b), the phenol from (6a) (93.0 mg, 0.326 mmol) was reacted with p-nitrobenzyl bromide. Silica gel chromatography (ethyl acetate-hexane, 40:60 then 50:50) gave the desired product (126.7 mg, 94%) as a yellow glass. MS found: $(M+H)^+$ = 413.

(14b) Following a procedure analogous to (1e), the ester from (14a) (120 mg, 0.291 mmol) was reacted with hydroxylamine to give the hydroxamic acid (108.0 mg, 90%) as a solid. MS found: $(M-H)^-$ = 412.

Example 15

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-3-[4-[(1-naphthalenyl)methoxy]phenyl]-2-oxo-1-pyrrolidineacetamide

(15a) Following a procedure analogous to (6b), the phenol from (6a) (115.6 mg, 0.417 mmol) was reacted with 2-bromomethylnaphthalene and cesium carbonate. Silica gel chromatography (ethyl acetate-hexane, 35:65 then 45:55) gave the desired product (168.5 mg, 97%) as a white solid. MS found: $(M+H)^+$ = 418.

(15b) Following a procedure analogous to (1e), the ester from (15a) (162.4 mg, 0.389 mmol) was reacted with hydroxylamine to give the hydroxamic acid (140.1 mg, 86%) as a white powder. MS found: $(M-H)^-$ = 417.

Example 16

[1(*R*)]-*N*-hydroxy-3-(4-hydroxyphenyl)- α,3-dimethyl-2-oxo-1-pyrrolidineacetamide

(16a) A mixture of the hydroxamic acid from (1e) (163.3 mg, 0.44 mmol), 20% palladium hydroxide on carbon (40.8 mg) and methanol (6 mL) was stirred under balloon pressure hydrogen for 1 h. Filtration and concentration of the filtrate gave

the hydroxamic acid (117 mg, 95%) as a white solid. MS found: $(M-H)^-$ = 277.

(16b) Following a procedure analogous to (16a), the product from (1f) (45.2 mg, 123 mmol) was hydrogenolyzed to furnish the hydroxamic acid (34.1 mg, 100%) as a white solid. MS found: $(M-H)^-$ = 277.

Example 17

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-2-oxo-3-[4-[(2-pyridinyl)methoxy]phenyl]-1-pyrrolidineacetamide

(17a) Cesium carbonate (306 mg, 2.8 eq) was added to the phenol from (6a) (92.8 mg, 0.335 mmol), and 2-picolyl chloride hydrochloride (110 mg, 2 eq) in methyl sulfoxide (2 mL). After 20 h at rt, same portions of cesium carbonate and 2-picolyl chloride were added. After 1 h at 50 °C, saturated ammonium chloride (6 mL) and ethyl acetate (100 mL) were added. The mixture was washed with water (6 mL), brine (6 mL), dried (MgSO4) and concentrated. Silica gel chromatography (ethyl acetate-hexane, 80:20 then 100:0) gave the desired product (112.7 mg, 91%) as a colorless oil. MS found: $(M+H)^+$ = 369.

(17b) Following a procedure analogous to (1e), the ester from (17a) (106.6 mg, 0.289 mmol) was reacted with hydroxylamine to give the hydroxamic acid (86.4 mg, 81%) as a white solid. MS found: $(M-H)^-$ = 368.

Example 18

[1(*R*)]-*N*-hydroxy- α,3-dimethyl-2-oxo-3-[4-[(3-pyridinyl)methoxy]phenyl]-1-pyrrolidineacetamide

(18a) Cesium carbonate (311 mg, 2.8 eq) was added to the phenol from (6a) (94.7 mg, 0.341 mmol), and 3-picolyl chloride hydrochloride (112 mg, 2 eq) in methyl sulfoxide (2 mL). After 20 h at rt, same portions of cesium carbonate and 3-picolyl chloride hydrochloride were added. After 2 h at 75 °C, saturated ammonium chloride (6 mL) and ethyl acetate (100 mL) were added. The mixture was washed with water (6 mL), brine (6 mL), dried ($MgSO_4$) and concentrated. Silica gel chromatography (ethyl acetate-hexane, 80:20 then 100:0) gave